

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 January 2003 (09.01.2003)

PCT

(10) International Publication Number
WO 03/002560 A1

(51) International Patent Classification⁷: **C07D 413/14**,
A61K 31/422, A61P 31/04, C07D 471/04

(21) International Application Number: PCT/IB02/02408

(22) International Filing Date: 24 June 2002 (24.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 0101559 27 June 2001 (27.06.2001) ES

(71) Applicant (for all designated States except US): **VITA-INVEST, S.A.** [ES/ES]; Fontsanà, 12-14, E-08970 Sant Joan Despi (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MOURELLE MANCINI, Marisabel** [ES/ES]; Av. Xile, 28, E-08028 Barcelona (ES). **HUGUET CLOTET, Juan** [ES/ES]; Riera Nofre, 11-13, E-08970 Sant Joan Despi (ES). **HIDALGO RODRIGUEZ, Jose** [ES/ES]; Calderon de la Barca, 99 bis 1^a 2^a, E-08914 Badalona (ES). **DEL CASTILLO, Juan Carlos** [—/ES]; Castillejos 389 1^a 1^a, E-08025 Barcelona (ES).

(74) Agents: **PONTISALES, Adelaida et al.**; Consell de Cent, 322, E-08007 Barcelona (ES).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),

Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

(57) Abstract: This invention discloses new fluorquinolonic derivatives of oxazolidinones of general formula (I) and processes for obtaining them, the corresponding pharmaceutical compositions and use thereof for manufacturing a medicament for the treatment of microbial infections. These new compounds are useful as antibacterial agents. Formula (I). Furthermore phenalen-type compounds according to general formula (II) are disclosed. Formula (II).

WO 03/002560 A1

NEW DERIVATIVES OF OXAZOLIDINONES AS ANTIBACTERIAL AGENTS

Field of the invention

This invention relates to fluorquinolonic
5 derivatives of oxazolidinones. The compounds are useful as
antibacterial agents.

Background of the invention

For some years now the pharmaceutical industry has
10 not been pursuing the development of new antibacterial
agents specifically directed at gram-positive bacteria
such as *Staphylococci*, *Enterococci*, *Streptococci* and
mycobacteria. The gram-positive bacteria have nevertheless
taken on particular importance due to the fact that they
15 have developed resistance at an alarming rate to the
conventionally used antibiotics, thus becoming organisms
difficult both to treat and to eradicate from hospital
environments. Examples of such strains are the
Staphylococcus resistant to *meticillin* (MRSA),
20 *Enterococcus* resistant to *vancomycin* (VRE), *Staphylococcus*
epidermidis resistant to *meticillin* (MRSE), *Staphylococcus*
pneumoniae resistant to *penicillin* (PRSP), etc.

The oxazolidinonic antibacterial agents are the
25 most recent class of synthetic drugs which show high
activity against gram-positive organisms. Owing to their
new action mechanism, these compounds are effective
against both sensitive and resistant pathogens, including
MRSA, MRSE and VRE.

30

Various antibacterial oxazolidinones have been
described in the patent literature, for example, to cite
some of them, in WO 9507271. WO 9323384, WO 9854161. WO
9514684, WO 9721708, WO 9514684, WO 9730981. WO 9737980.

WO 9801447, WO 9912914, WO 9613502.

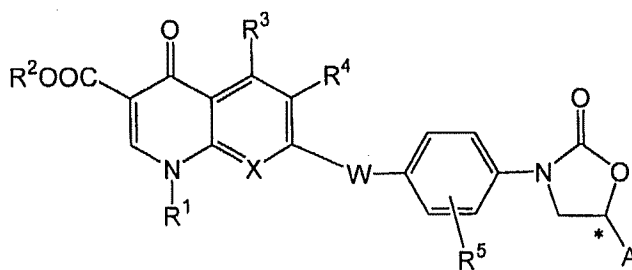
All these patents describe the oxazolidinones as compounds active against resistant gram-positive 5 organisms.

Owing to the constant appearance of new resistances, even to recently used antibiotics, it is desirable to develop powerful new antibiotics active 10 against the resistant strains, preferably with a broad antimicrobial spectrum.

This invention provides new derivatives of oxazolidinones, with a broad antimicrobial spectrum due to 15 their being active against gram-negative organisms while having improved activity against gram-positive organisms.

Description of the invention

20 The object of this invention are new fluorquinolonic derivatives of oxazolidinones of general formula (I):



25

(I)

in which:

X: CR⁶ or N;

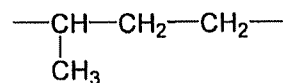
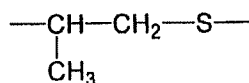
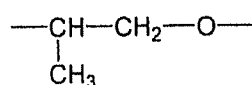
R¹: alkyl C₁-C₄, cycloalkyl C₃-C₆, alkenyl C₂-C₄, 2-hydroxyethyl, 2-fluoroethyl, or phenyl optionally substituted by 1 or 2 atoms of fluorine;

R²: H, alkyl C₁-C₄ or phenyl;

10 R³: H, halogen, alkyl C₁-C₄, or alkoxy C₁-C₄, amino;

R⁴: H or halogen;

15 R⁶: H, halogen, alkyl C₁-C₄, haloalkoxy C₁-C₄, or else R¹ and R⁶ together form a bridge of structure



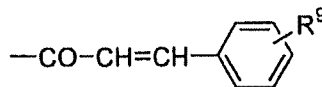
20 R⁵: H, halogen, OCH₃, alkoxy C₁-C₄, alkyl C₁-C₄, or haloalkyl C₁-C₄;

A: -CH₂-NH-R⁷, -CHOH-C≡CH;

25

in which

R⁷: isoxazol, -CO-R⁸, -CS-R⁸, -CS-OR⁸, -COOR⁸, -CONHR⁸, -CSNHR⁸, -SO₂-R⁸ or



30

in which

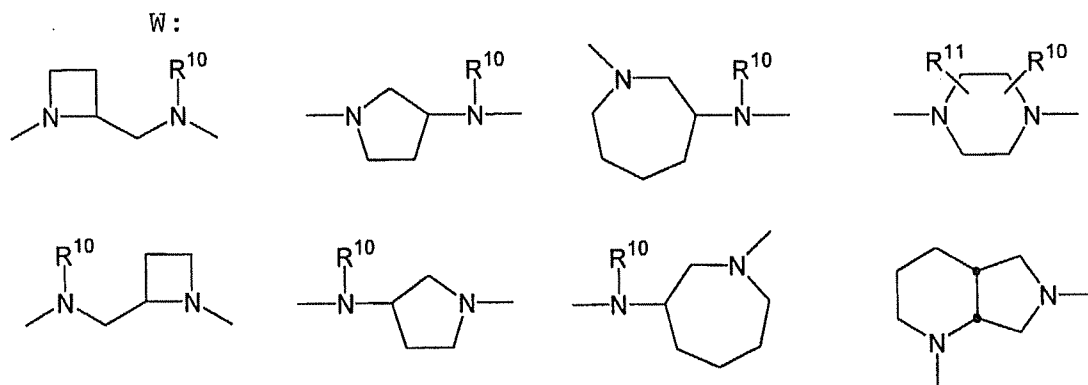
R^8 : alkyl C_1-C_4 , haloalkyl C_1-C_4 , alkenyl C_2-C_4 , aryl, alkyl C_1-C_4 substituted by an alkoxy group C_1-C_4 , carboxyalkyl C_1-C_4 , cyano, or amino, ...

5

R^9 : H, alkyl C_1-C_4 , alkenyl C_2-C_4 , OH, alkoxy C_1-C_4 , $NR^{12}R^{13}$, NO_2 , halogen, or $CO-R^{12}$;

R^{12} and R^{13} : independently, H or alkyl C_1-C_4 ;

10



in which

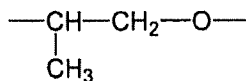
R^{10} and R^{11} are independently H, or alkyl C_1-C_4 ;

15

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

20

Preferably, R^1 is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else R^1 and R^6 together form a bridge of structure:

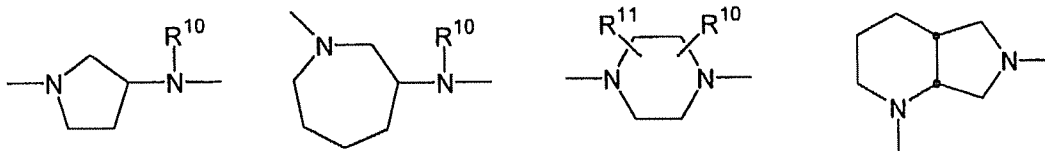


Preferably, R^6 is H, CH_3 , OCH_3 , $OCHF_2$, F or Cl.
More preferably, R^6 is H or F.

Preferably, R^4 is F or Cl and R^3 is H.

5

Preferably, W is



in which R^{10} and R^{11} are as defined previously.

10

The compounds of the invention have a chiral centre in position C5 of the oxazolidinone ring. The preferred configuration of the C5 of the oxazolidinone ring is (S) for the compounds of formula (I) in which A = -
15 CH_2-NH-R^7 and (R) for the compounds of formula (I) in which A = $-CHOH-C\equiv CH$, in accordance with the Cahn-Ingold-Prelog nomenclature system.

Moreover, the compounds of formula (I) can contain
20 other chiral centres. It is understood that the invention includes such optical isomers and diastereoisomers and mixtures thereof that possess antibacterial activity in any proportion.

25 The preferable compounds are selected from one of the following:

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-
30 fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 15 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 30 - 1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-

- 3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 5 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 10 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 20 - 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 25 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 30 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 10 - 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 15 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-(methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 30 - 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-
10 difluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-
15 difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl
20 ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
25 dihydro-6H-1-oxa-3a-aza-phenalen-5- carboxylic acid methyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
30 dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-

- fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5- carboxylic acid methyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-
 - 5 fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-
 - 10 carboxylic acid methyl ester
 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid ethyl ester
 - 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 20 ethyl ester
 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
 - 25 carboxylic acid methyl ester
 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
 - 30 carboxylic acid ethyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid methyl ester

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3- carboxylic acid methyl ester
- 5 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10 In this invention the term "a pharmaceutically acceptable solvate" is taken to mean a hydrate or solvate of an alcohol C₁-C₄.

 In this invention, the term "pharmacologically
15 acceptable salts" includes salts of alkaline metals such as sodium or potassium and salts of alkaline earth metals such as calcium or magnesium, as well as acid-addition salts formed with inorganic and organic acids such as hydrochlorides, hydrobromides, sulphates, nitrates,
20 phosphates, formiates, mesylates, citrates, benzoates, fumarates, maleates, lactates and succinates, among others.

 The pharmacologically acceptable salts are
25 prepared by reaction of a compound of formula (I) with a suitable quantity of a base such as sodium, potassium, calcium or magnesium hydroxyde, or sodium methoxide, sodium hydride, potassium tert-butoxyde and the like in solvents such as ether, THF, methanol, ethanol, tert-
30 butanol, isopropanol, dioxane, etc., or else in a mixture of solvents. The addition salts, where applicable, can be prepared by treatment with acids, such as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric, formic, methanesulphonic, citric, benzoic, fumaric, maleic, lactic

and succinic, in solvents such as ether, alcohols, acetone, THF, ethyl acetate, or mixtures of solvents.

The stereoisomers of this invention can be
5 prepared by using reagents in a single enantiomeric form in processes where this is possible or by carrying out the reaction in the presence of reagents or catalysts in their single enantiomeric form or by resolution of mixtures of stereoisomers by conventional methods. Some of the
10 preferred methods include resolution of diastereoisomeric salts formed with chiral acids such as mandelic, camphorsulphonic, tartaric acid and the like. Methods commonly used are included in Jaques et al. in "Enantiomers, Racemates and Resolution" (Wiley
15 Interscience, 1981).

In the definitions of this invention, an alkyl group C_1-C_4 , as a group or as part of a group, is taken to mean a lineal or branching alkyl group which contains up
20 to 4 atoms of carbon. Thus it includes, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and tert-butyl.

Likewise, an alkoxy group C_1-C_4 includes, for
25 example, a methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy and tert-butoxy group.

An alkenyl group C_2-C_4 includes, for example, a vinyl, allyl, propenyl and 1-butenyl, 2-butenyl and 3-
30 butenyl group.

A haloalkyl group C_1-C_4 means an alkyl group C_1-C_4 substituted by one or more atoms of halogen, the same or different. It thus includes, for example, chloromethyl,

fluoromethyl, trifluoromethyl, chloroethyl, fluoroethyl, difluoroethyl, trifluoroethyl, fluoropropyl, chloropropyl, etc.

5 A haloalkoxy group C₁-C₄ means an alkoxy group C₁-C₄ substituted by one or more atoms of halogen, the same or different. Thus it includes, for example, chloromethoxy, fluoromethoxy, trifluoromethoxy, chloroethoxy, fluoroethoxy, difluoroethoxy, 10 trifluoroethoxy, fluoropropoxy, chloropropoxy, etc.

A cycloalkyl group C₃-C₆ represents a cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl group.

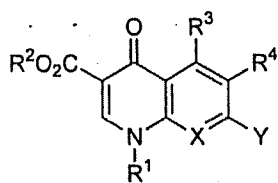
15 The term halogen, in this invention, refers to F, Cl, Br, I, preferably F and Cl.

The term aryl, in this invention, includes phenyl and naphthyl optionally substituted by up to five 20 substituents, the same or different, preferably up to two, in any position of the ring. Suitable substituents include halogen, amino, hydroxy, alkyl C₁-C₄, alkoxy C₁-C₄, phenyl.

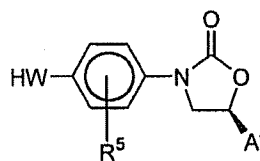
The compounds of this invention can be prepared in 25 various ways. They can be prepared by using the methods described below, together with methods known in the field of organic chemical synthesis, or by the variations that might be made thereto by an expert in the subject. Preferred methods include, but are not limited to, those 30 described below. The reactions are carried out in the solvents appropriate for the reagents and materials used and suited for the transformations carried out. An expert in organic synthesis will understand that the functional groups present in the molecule must be consistent with the

proposed transformations. This may in some cases require modifying the order of the synthesis steps or selecting one particular method rather than another, in order to obtain the desired compound of the invention. Moreover, in some of the procedures described below it may be desirable or necessary to protect the reagent functional groups present in the compounds or intermediates of this invention with conventional protecting groups. Various protecting groups and procedures for introducing them and removing them are described in Greene and Wuts (*Protective Groups in Organic Synthesis*, Wiley and Sons, 1999). All the references cited herein are incorporated integrally by reference.

The compounds of formula (I) can be obtained by reaction of a compound of formula (II), with a compound of formula (III):



(II)



(III)

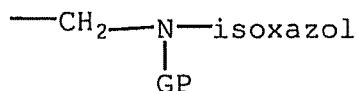
in which

A' is:

a) $-\text{CH}_2-\text{NH}-\text{R}^7$

b) $-\text{CHOH}-\text{C}\equiv\text{CH}$

c)



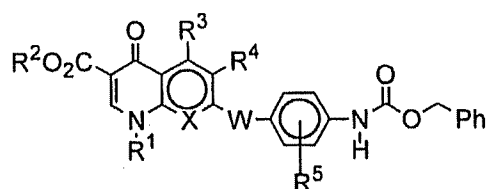
25

Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like; R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined

above;

GP is an amine protecting group.

Alternatively, the compounds of formula (I) in 5 which A= -CHOH-C≡CH can also be obtained by reaction of a compound of formula (IV) with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate:

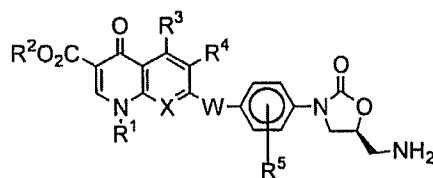


10

(IV)

in which R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above.

The compounds of formula (I) in which A= -CH₂-NH-R⁷ 15 and R⁷ is different from isoxazol, can also be obtained by reaction of a compound of formula (V):



(V)

20

in which R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above, with a compound of formula (VI) or with a compound of formula (VII)

25

R⁷-L
(VI)

R⁸-N=C=Z
(VII)

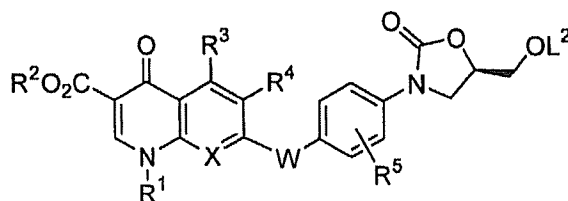
in which

L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group and the like;

Z is Oxygen or Sulphur, and

R⁷ and R⁸ have the meaning defined above, with R⁷ being different from isoxazol.

- 10 The compounds of formula (I) in which A = -CH₂-NH-R⁷ and R⁷ is isoxazol can also be obtained by reaction of a compound of formula (VIII)



(VIII)

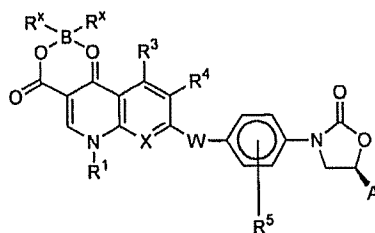
- 15 in which

- OL² represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, whether substituted or not substituted, preferably by a tosylate or mesylate group;

- 20 - R¹, R², R³, R⁴, R⁵, X and W have the meaning defined above;

with isoxazolil-3-amine, with the amino group suitably protected with an amine protecting group, for example with Troc (2,2,2-trichloroethoxycarbonyl).

The compounds of formula (I), in which R² = H can also be obtained by hydrolysis of a boron chelate of formula (IX):



(IX)

in which

5 R^x can be F or CH_3COO^- ;

A, R^1 , R^3 , R^4 , R^5 , X and W have the meaning defined above.

And if required, after any of the methods
10 described herein, one or more of the following optional steps can be carried out:

- Converting a compound of general formula (I) into another compound of general formula (I);
- Eliminating any protecting group;
- 15 - Preparing a pharmacologically acceptable salt of a compound of formula (I) and/or pharmacologically acceptable solvate thereof.

The reaction of the compounds of formula (II) with
20 compounds of formula (III) is carried out in an organic solvent in the presence of an organic base. Preferably the reaction is carried out in solvents such as pyridine, acetonitrile, dimethylformamide, N-methylpyrrolidone, etc. in the presence of bases such as triethylamine, DBU,
25 diisopropylethylamine, etc.

The reaction of compounds of formula (IV) with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is carried out in an aprotic solvent such as N,N-dimethylformamide, THF,

preferably THF, at low temperature, preferably at -68°C , and in the presence of a base such as n-butyllithium, lithium tert-butoxide, LDA, preferably in n-butyllithium.

5 The reaction of compounds of formula (V) with a compound of formula (VI) is carried out in an organic aprotic solvent such as acetonitrile, dichloromethane or pyridine or in a mixture of an organic solvent and water in the presence of a base. Preferably L is Cl, EtO, etc,
10 so that $\text{R}^7\text{-L}$ can be an acid, an acid chloride, an anhydride, an ester, a dithioester, an alkyl or aryl chloroformate, etc. The reaction of compounds of formula (V) with a compound of formula (VII) is preferably carried out in pyridine.

15

 The reaction of the compounds of formula (VIII) with isoxazolil-3-amine, with the amino group suitably protected, is carried out in an aprotic solvent such as N,N-dimethylformamide, N,N-dimethylacetamide, preferably
20 in N,N-dimethylformamide, at a temperature between 0 and 70°C , and in the presence of a strong base such as sodium hydride, lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide or sodium amide, preferably sodium hydride.

25

 Hydrolysis of the compounds of formula (IX) can be carried out according to the methods previously described in the literature (Masuhiro Fujita Chem. Pharm. Bull. (1988), 46(5), 787-796, Joseph P. Sánchez J. Med.
30 Chem. (1995), 38, 4478-4487)

 For $\text{R}^* = \text{F}$, the hydrolysis is carried out preferably in a mixture of alcohol-water in the presence of a base. As water-alcohol mixture it is preferable to

use ethanol-water or methanol-water and as base it is preferable to use an organic base such as triethylamine or another secondary or tertiary amine such as tributylamine, diisopropylethylamine, DBU, etc. The reaction is carried out at a temperature that can range between room temperature and the reflux temperature of the water-alcohol mixture. The reaction is carried out preferably at the reflux temperature of the water-alcohol mixture.

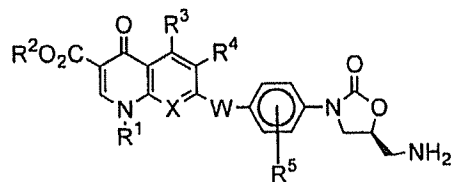
- 10 When $R^* = CH_3COO$ the hydrolysis is carried out preferably in a mixture of an organic aprotic solvent and another protic solvent in the presence of a base. As aprotic solvent it is preferable to use acetonitrile and as protic solvent it is preferable to use water. As base
15 it is preferable to use an inorganic base such as sodium, lithium or potassium hydroxide or sodium, lithium or potassium carbonate, etc.

A reaction of interconversion of a compound of
20 formula (I) into another compound of formula (I) consists, for example, in hydrolysing a compound of formula (I) in which R^2 is an alkyl C_1-C_4 or phenyl radical to convert it into a compound of formula I in which R^2 is hydrogen. The hydrolysis is carried out preferably in a water-alcohol
25 medium preferably using as base an inorganic base. Still more preferably, the hydrolysis is carried out in ethanol-water or methanol-water, while sodium, lithium or potassium hydroxide is used as a base.

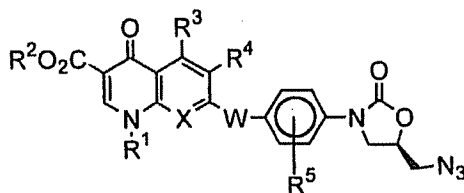
Another example of reaction of interconversion of
30 a compound of formula (I) in another compound of formula (I) consists in the esterification of a compound of formula (I) in which R^2 is hydrogen, to yield another compound of formula (I) in which R^2 is an alkyl C_1-C_4 or phenyl radical, by the conventional methods of

esterification described in the literature. For example, by reaction of a compound of formula R^2-OH with the compound of formula (I) in which R^2 is hydrogen, having previously activated the carboxylic acid with carbonyl 5 diimidazole, or else having previously converted the carboxylic acid into an acid chloride by reaction with thionyl chloride, or else having converted it into mixed anhydride by reaction with alkyl chloroformate.

Also object of invention are the compounds of 10 formula (V), (X) and (XI):

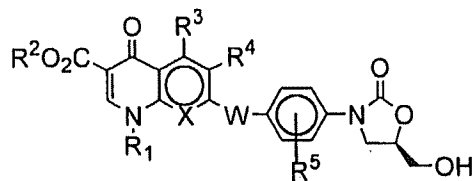


(V)



(X)

15



(XI)

in which R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined above. These compounds are useful as 20 intermediates for making the compounds of formula (I) of

this invention.

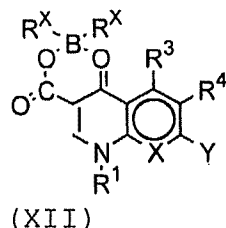
Described below are some of the procedures for making the intermediates used for preparing the compounds 5 of formula (I).

The compounds of formula (V), (X) and (XI) can be obtained in accordance with schemes 1A and 1B.

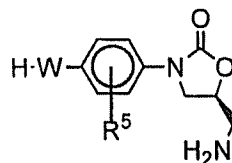
10 Thus, the compounds of formula (V) can be obtained:

a. by reaction of a compound of formula (II) or of formula (XII) with a compound of formula (XIII):

15



(XII)



(XIII)

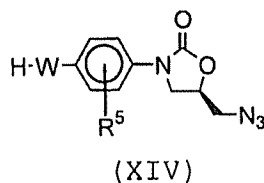
20

The reaction can be carried out under the conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b. by catalytic reduction of a product of formula 25 (X) or by reduction of the azide group chemically with triphenylphosphine, etc.

The compounds of formula (X) can in their turn be obtained:

30 a. by reaction of a compound of formula (XII) or of formula (II) with a compound of formula (XIV):

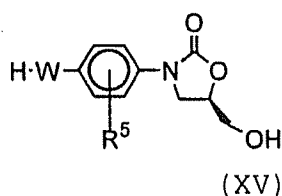


The reaction can be carried out under the 5 conditions described above for the reaction of a compound of formula (II) with a compound of formula (III);

b. from a compound of formula (XI) by conversion of the hydroxyl group into a good leaving group, such as mesylate, tosylate or halogen and subsequent reaction with 10 sodium azide.

The compounds of formula (XI) can in their turn be obtained:

a.- by reaction of a compound of formula (XII) or 15 of formula (II) with a compound of formula (XV):



The reaction can be carried out under the conditions described above for the reaction of a compound 20 of formula (II) with a compound of formula (III);

b.- by reaction of a compound of formula (IV) with (R)-glycidil butirate. The reaction is carried out in an aprotic solvent such as N,N-dimethylformamide, THF, preferably THF, at low temperature, preferably at -68°C, 25 and in the presence of a base such as n-butyllithium, lithium tert-butoxide, LDA, preferably in n-butyllithium.

Utilisation of the compounds of formula (XII) to obtain the three foregoing intermediates requires an additional step of hydrolysis of the boron chelate, as indicated in schemes 1A and 1B, which step is carried out 5 under the conditions described above for hydrolysis of the compound of formula (IX).

The compounds of formula (VIII) can be obtained by reaction of a compound of formula (XI) with aryl or methyl 10 sulphonyl chloride, substituted or not substituted, preferably with mesyl chloride or p-toluenesulphonyl chloride, in an aprotic solvent, such as methylene chloride, and in the presence of an organic base, such as triethylamine.

15

The compounds of formula (IX) can be obtained by reaction of a compound of formula (XII) with a compound of formula (III). The reaction can be carried out under the conditions described above for the reaction of a compound 20 of formula (II) with a compound of formula (III).

The products of formula (II) and of formula (XII) are obtained according to the methods described in the literature. This products have been used as intermediates 25 in the synthesis of quinolones and similar with antibacterial activity such as cyprofloxacin, ofloxacin, moxyfloxacin, norfloxacin, tosufloxacin, etc. (See patents WO 8807993, WO 8807998, WO 9006922, JP 59122470. JP 58029789, EP 0351889).

30

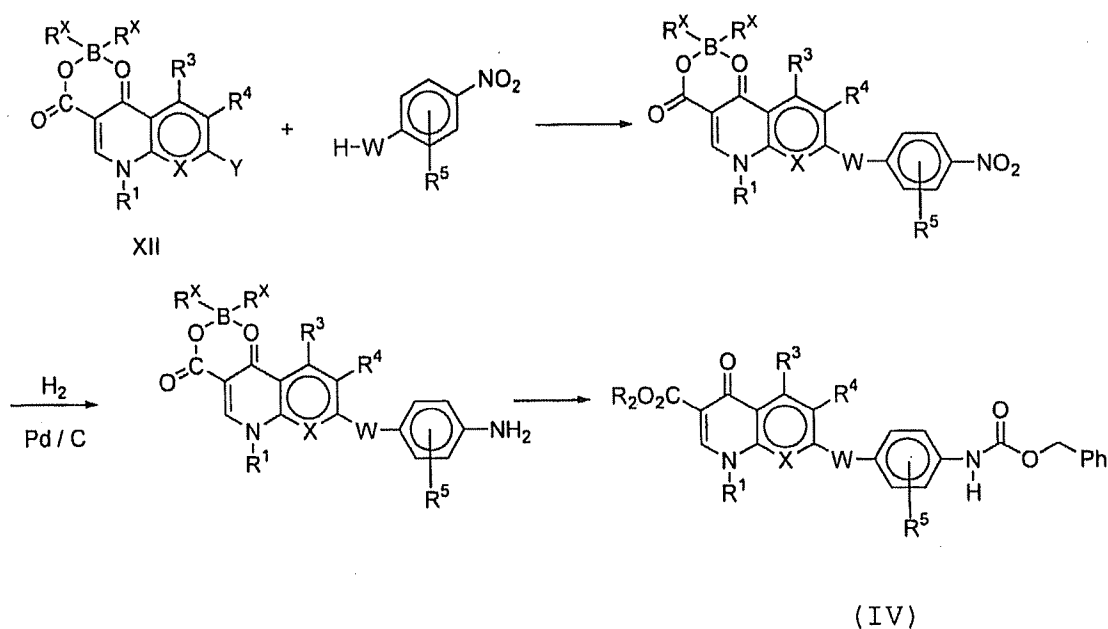
The compounds of formula (III), (XIII), (XIV) and (XV) can be obtained in accordance with scheme 2.

Thus, the compounds of formula (IIIa), (XIII) and (XIV) can be obtained from a compound of formula (XVI) by conversion of the hydroxyl group into an NH_2 , N_3 or NHR^7 group, in accordance with reactions well-known to an expert in organic chemistry.

The compounds of formula (IIIb) can be obtained by reaction of a compound of formula (XVII) with 2,3-hydroxypent-4-ynyl p-toluenesulphonate, under conditions analogous to those described for the reaction of a compound of formula (IV) with said reagent.

The compounds of formula (IIIc) can be obtained by reaction of a compound of formula (XVI) with isoxazolil-3-amine, with the amino group suitably protected, for example with Troc, and prior conversion of the hydroxyl group into a good leaving group, for example, mesylate, tosylate, halogen, etc.

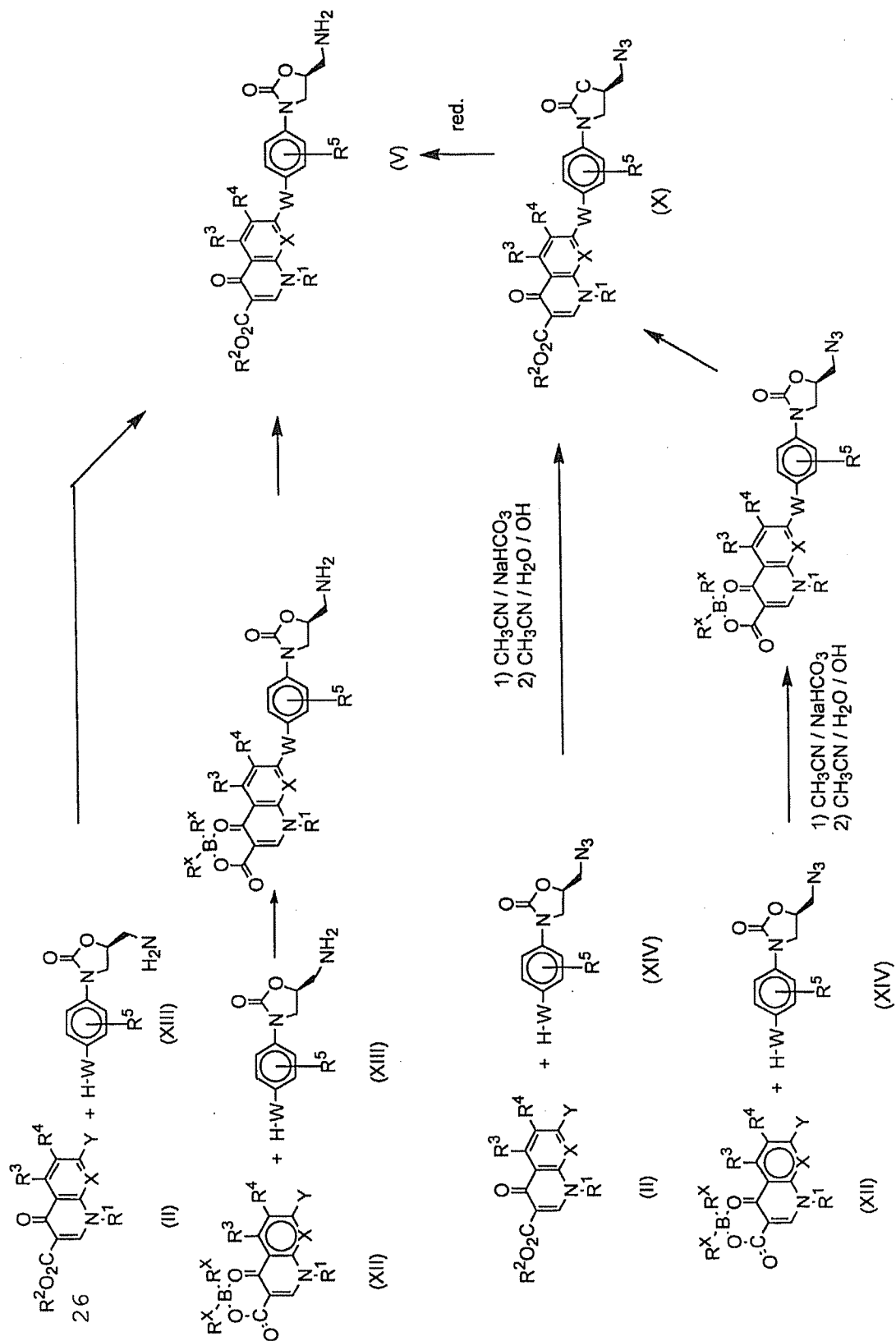
20 The compounds of formula (IV) can be obtained according to the following scheme:



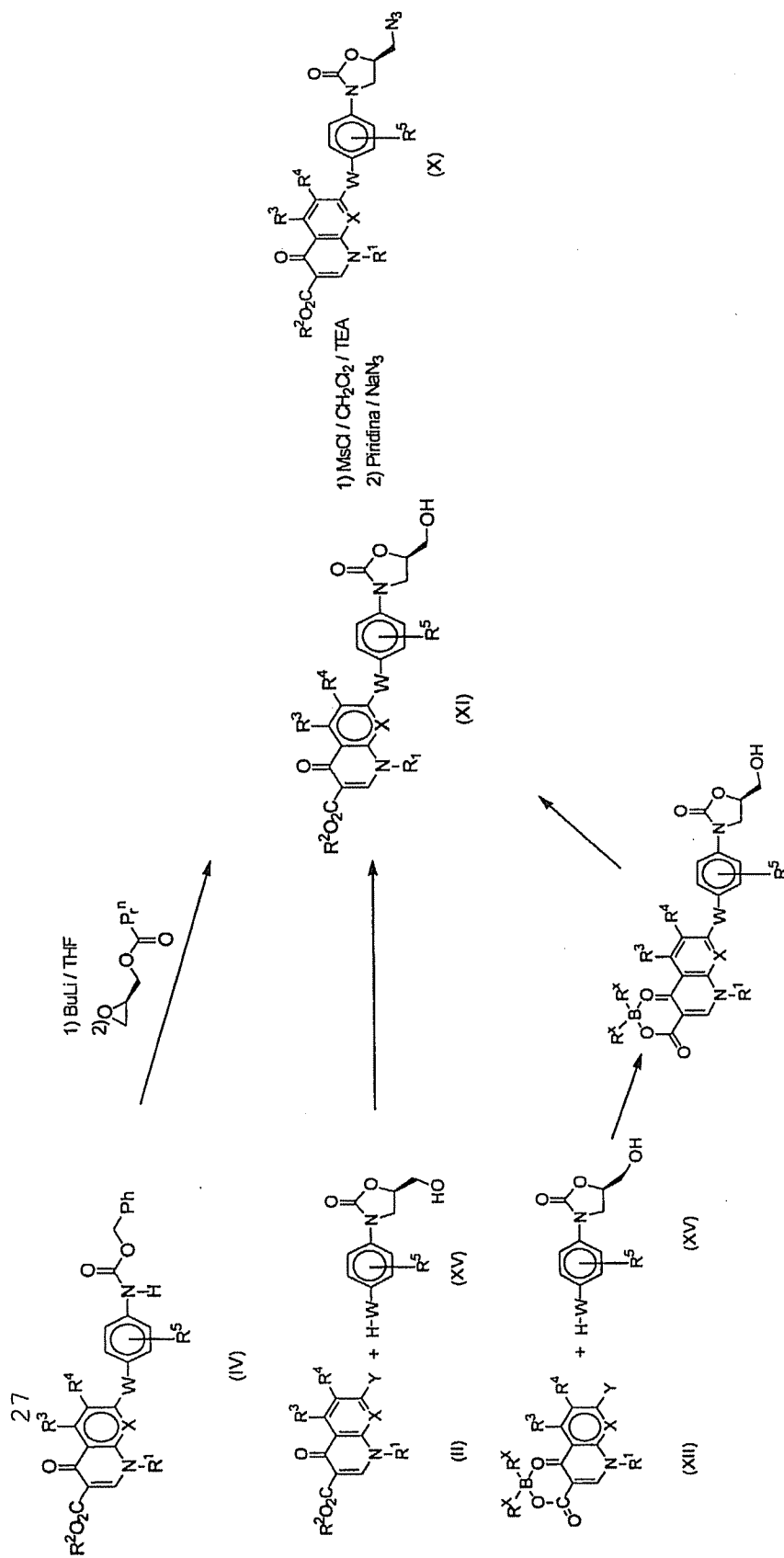
The reactions are carried out in suitable solvents, 5 and under conventional conditions. The schemes indicate the preferred reaction conditions.

The 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate is obtained according to the procedure described in EP 10 1029854A1.

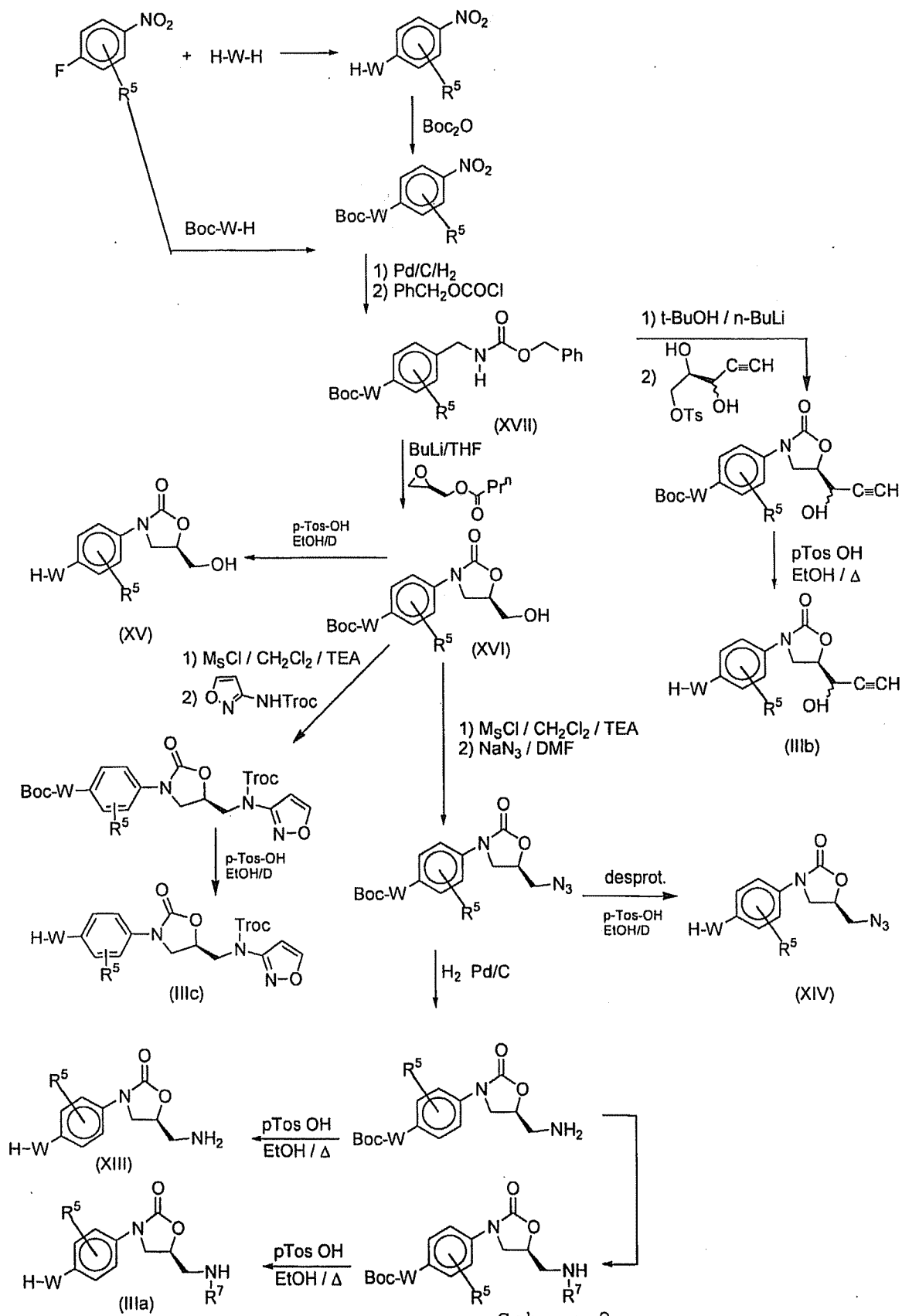
The compounds of formula (VI) and of formula (VII) are commercial, are extensively described in the literature or can be prepared by methods analogous to 15 those known in the state of the art from products commercially available.



Scheme 1A



Scheme 1B



Scheme 2

Also object of this invention are compositions which include a compound of general formula (I), a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers
5 thereof in any proportion or polymorph thereof, in a therapeutically active quantity and a suitable quantity of at least one pharmacologically acceptable excipient.

The compositions of the invention can be
10 formulated in solid or liquid form following the conventional pharmaceutical techniques. The solid formulations include tablets, capsules, sachets, powders, suppositories, etc. The excipients can include diluents, disintegrators, wetting agents, lubricants, colourants,
15 flavourings or other conventional adjuvants. The typical solid excipients include, for example, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium stearate or sodium lauryl sulphate. The liquid compositions include solutions, suspensions or emulsions.
20 They can consist in solutions in water or in water-propyleneglycol or water-polyethylenglycol systems, also optionally containing flavourings, colourants, stabilisers and thickeners.

25 The compositions can be administered orally, parenterally or topically.

The compounds of formula (I) show activity as antibacterial agents. Advantageously they possess a broad
30 spectrum of activity against gram-positive bacteria such as *Staphylococcus*, *Streptococcus*, *Enterococcus* and the like, as well as against gram-negative bacteria such as *E. Coli*, *H. Influenzae*, *M. catarrhalis*, etc., and even against strains resistant to known antibiotics such as

meticillin, vancomicine, penicillin, etc. They are also active against anaerobic microorganisms such as *Bacteroides fragilis*. Also object of this invention, therefore, is the use of a compound of formula (I) for making a pharmaceutical composition for the treatment of microbial infections, in humans or warm-blooded animals.

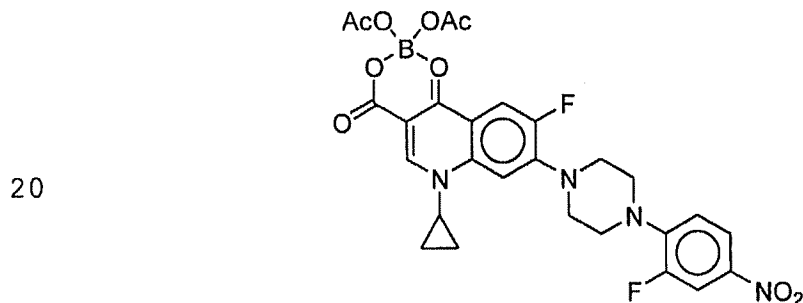
Below, and by way of non-restrictive explanation of the invention, the following examples are set out.

10 EXAMPLES OF SYNTHESIS

PREPARATION OF INTERMEDIATES

Reference Example No.1:

1-Cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-nitro-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-
15 carboxylic acid diacethoxyboron chelate



To 10 g (0.024 mol) of 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 150 ml of acetonitrile are added 5.4 g (0.024 mol) of 1-(2-fluoro-4-nitro-phenyl)piperazine (obtained according to the method described by S.J. Brickner and col. J. Med. Chem. 1996, 39, 673-679) and 2 g (0.024 moles) of sodium bicarbonate.

The reaction is heated to reflux for 48 h. It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of

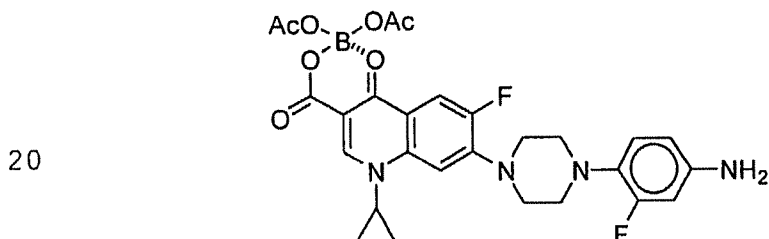
dichloromethane. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol 98/2 yields 6.7 g of the product of the title.

¹H-RMN: (CDCl₃, 200 MHz, δppm): 9,08 (s, 1H); 8,14 (d, 1H); 8,10-7,94 (s.c., 2H); 7,56 (d, 1H); 7,01 (t, 1H); 3,82-3,75 (m, 1H); 3,75-3,50 (s.c., 8H); 2,04 (s, 6H); 1,64-1,30 (s.c., 4H).

Reference Example No.2:

7-[4-(4-amino-2-fluoro-phenyl)piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate.



To 6.7 g (0.011 mol) of the product obtained in the previous example, in 50 ml of dimethylformamide, are added 0.7 g of 10% Pd/C paste and it is placed under hydrogen atmosphere at 40°C and atmospheric pressure. When the reaction has finished it is filtered over decalite and the decalite washed with 20 ml of DMF.

30

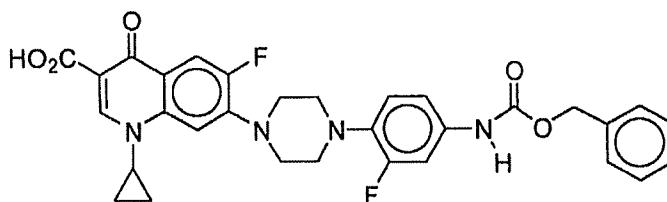
The filtrate liquids are poured onto 700 ml of water and extracted with 3 x 200 ml of dichloromethane. The organic phase is concentrated to dryness and the residues chromatographed on silica gel.

Elution with dichloromethane-ethanol 95/5 yields 2.6 g of the product of the title as yellow solid.

¹H-RMN (CDCl₃, 200 MHz, δ(ppm)): 9,04 (s, 1H); 8,10 (d, 1H); 7,45 (d, 1H); 6,84 (dd, 1H); 6,44-6,36 (s.c., 2H); 3,79-3,64 (m, 1H); 3,62-3,56 (s.c., 4H); 3,24-3,16 (s.c., 4H); 2,05 (s, 6H); 1,80-1,20 (s.a., 2H, NH₂); 1,58-1,24 (s.c., 4H).

Reference Example No.3:

7-[4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



To 2.62 g (4.58 mmol) of the product obtained in the previous reference example in 30 ml of THF and 10 ml of water is added 0.4 g (5 mmol) of sodium bicarbonate.

Onto the previous solution is added dropwise 0.8 g (5 mmol) of benzyl chloroformate and is maintained with stirring for 48 h. It is concentrated to dryness, 50 ml of water are added and it is extracted with 3 x 75 ml of dichloromethane.

The organic phase is dried and concentrated. The residue is stirred with 10 ml of dichloromethane for 10 minutes and the precipitate obtained is filtered.

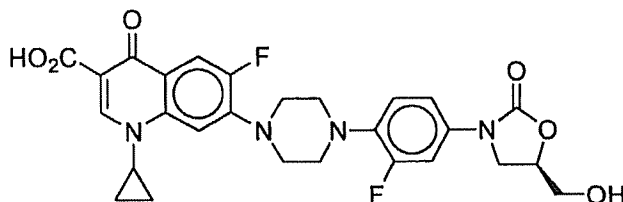
2 g of the product of the title are obtained thereby.

^1H -RMN (DMSO, 200 MHz, δ (ppm)): 9,84 (s.a., 1H); 8,64 (s, 1H); 7,92 (d, 1H); 7,61 (d, 1H); 7,50-7,30 (s.c., 6H); 7,22-7,01 (s.c., 2H); 5,18 (s, 2H); 3,92-3,78 (s.a., 5 1H); 3,70-3,10 (s.c., 8H); 1.42-1.10 (s.c., 4H).

Reference Example No.4:

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

15



20 To 2.2 g (3.7 mmol) of the product obtained in the previous preparation in 60 ml of THF cooled to -78°C is added dropwise 3 ml (7.14 mmol) of n-butyllithium 2.5 M in hexane.

25 The reaction is maintained at -78°C for 1 h and then 0.51 g (3.57 mmol) of (R)-glycidil butirate dissolved in 10 ml of THF are added.

It is allowed to reach room temperature and stirred thus 30 for 16 h.

20 ml of saturated solution of ammonium chloride is added and it is concentrated until the THF is removed. 50 ml of

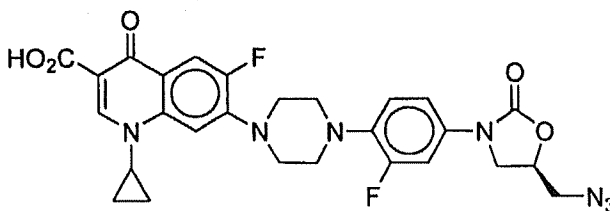
water are added and this is extracted with 3 x 100 ml of dichloromethane-ethanol (90/10).

The organic phase is dried and concentrated. The residue is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 0.5 g of the product of the title.

¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,70-7,36 (s.c., 3H); 7,30-7,10 (s.c., 2H); 5,20-5,10 (s.a., 1H); 4,8-4,64 (m, 1H); 4,20-4,04 (m, 1H); 3,92-3,14 (s.c., 11H); 1,43-1,16 (s.c., 4H).

Reference Example No.5:

15 7-{4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



20

Method 1:

To 0.5 g (0.92 mmol) of the product obtained in the previous preparation in 10 ml of dry dichloromethane is added 2.6 ml of triethylamine and it is then cooled to 0°C. 1.4 ml of methanesulphonyl chloride is added and this is then stirred at 0°C for 1 h.

It is poured onto water-ice (30 ml/20 g) saturated with sodium bicarbonate and the organic phase is decanted. It is dried on sodium sulphate, filtered and concentrated.

5 To the residue is added 10 ml of dimethylformamide and 1.17 g of sodium azide. This is heated to 75°C and stirred at this temperature for 16 h.

It is poured onto 100 ml of water and extracted with 3 x 100 ml of ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel. Elution with dichloromethane-ethanol (90/10) yields 40 mg of the product of the title.

15 Method 2:

To 1.5 g (4.7 mmol) of 5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one (Reference Example No.19) and 1.9 g (4.7 mmol) of acid 1-cyclopropyl-7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) in 60 ml of acetonitrile is added 0.4 g (4.7 mmol) of sodium bicarbonate and this is heated to reflux for 48 h.

25

It is concentrated to dryness and the residue is treated with 100 ml of water and extracted with 3 x 100 ml of CH₂Cl₂. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

30

Elution with CH₂Cl₂/EtOH 95/5 yields 1.1 g of the product of the title as diacetoxiboron chelate.

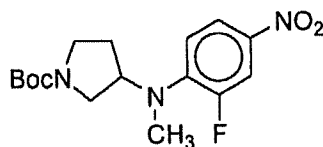
The 1.1 g thus obtained is dissolved in a mixture of 28 ml of water, 28 ml of acetonitrile and 8 ml of sodium hydroxide 1N. This is stirred at room temperature for 3 h, the acetonitrile is concentrated and 8 ml of hydrochloric 5 acid 1N is added.

The precipitated solid is filtered, yielding 0.6 g of product identical to that obtained by method 1.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,79 (s, 1H);
10 8,01 (d, 1H); 7,54-7,24 (s.c., 2H); 7,16-6,90 (s.c., 2H);
4,83-4,70 (m, 1H); 4,42-4,34 (m, 1H); 4,10-3,20 (s.c.,
12H); 1.44-1.12 (s.c., 4H)

Reference Example No.6:

15 3(R,S) - [(2-fluoro-4-nitro-phenyl)-methylamino] -
pyrrolidine-1-carboxylic acid tert-butyl ester



20

To 7 g (0.0375 mol) of 3(R,S)-methylamino-pyrrolidine-1-carboxylic acid tert-butyl ester and 4.11 ml (0.0375 mol) of 3,4-difluoronitrobenzene in 80 ml of DMF is added 3.15 g of sodium bicarbonate and this is heated at 45°C for 16
25 h.

It is poured onto 800 ml of water and extracted with 3 x 300 ml of AcOEt. The organic phase is dried and concentrated and the residue is chromatographed on silica
30 gel.

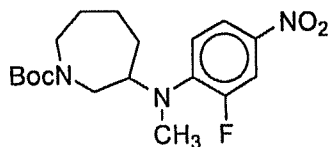
Elution with dichloromethane-ethanol 95/5 yields 7.9 g of the product of the title.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,00-7,88 (s.c, 2H); 6,88 (dd, 1H); 4,45-4,30 (m, 1H); 3,75-3,50 (s.a., 4H); 3,45-3,25 (s.c, 4H); 2,95 (s, 3H); 2,18-2,07 (m, 5 2H); 1.49 (s, 9H).

Reference Example No.7:

3(R, S)-[(2-fluoro-4-nitro-phenyl)-methyl-amino]-azepan-1- carboxylic acid tert-butyl ester.

10



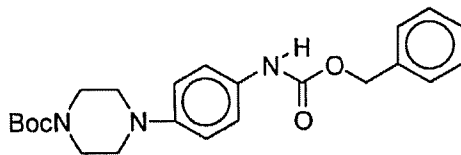
Following the previous procedure and using 3(R,S)-
15 methylamino-azepan-1-carboxylic acid tert-butyl ester, the product of the title is obtained.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,10-7,80 (m, 2H); 6,90 (dt, 1H); 4,05-3,10 (m, 5H); 2,94 (m, 3H); 1.50
20 and 1.41 (s, 9H); 1.20-2,10 (m, 6H).

Reference Example No.8:

4-(4-Benzylloxycarbonylamino-phenyl)-piperazin-1- carboxylic acid tert-butyl ester.

25



30

To 72.7 g (0.236 mol) of 4-(4-nitro-phenyl)-piperazin-1-
carboxylic acid tert-butyl ester (WO 9725323), in 600 ml
of THF and 125 ml of water is added 7.27 g of 10% Pd/C

paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature.

When reduction of the nitro group has been completed (thin-layer chromatography eluted with heptane/AcOEt 1/1), 5 21 g (0.25 mol) of sodium bicarbonate and 40.2 g (0.236 mol) of benzyl chloroformate are added at 0°C.

It is shaken for 30 min at 0°C and filtered over decalite. The decalite is washed with 300 ml of THF and the filtrate 10 liquids are concentrated until the THF has been removed.

200 ml of water is added and 3 x 200 ml of dichloromethane is extracted. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

15

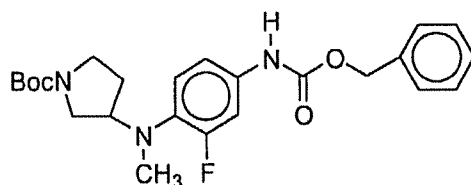
Elution with heptane/AcOEt yields 69.8 g (72%) of the product of the title.

20 ^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42-7,24 (s.c., 7H); 6,86 (d.2H); 6,64 (s.a., 1H); 5,18 (s, 2H); 4,60-4,50 (s.c., 4H); 3,10-3,00 (s.c., 4H); 1.46 (s, 9H).

Using the procedure described above the following products 25 are obtained:

Reference Example No.9:

3(R, S) - [(4-benzyloxycarbonylamino-2-fluoro-phenyl) - methyl-amino] - pyrrolidine-1- carboxylic acid tert-butyl
30 ester.



5

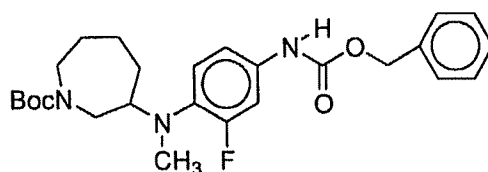
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,42-7,26 (s.c. 6H); 7,01-6,92 (s.c., 3H, 2H aromatic + NH); 5,19 (s, 2H); 3,86-3,65 (m, 1H); 3,60-3,36 (s.c., 3H); 3,36-3,12 (s.c., 2H); 2,71 (s, 3H); 2,10-1,75 (s.c., 2H); 1,42 (s, 9H).

10

Reference Example No.10:

3 (R, S) - [(4-benzyloxycarbonylamino-2-fluoro-phenyl) - methyl-amino] - azepan-1-carboxylic acid tert-butyl ester.

15



20

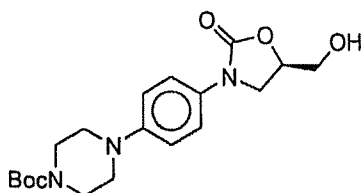
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,60-7,20 (m, 5H); 7,20-6,80 (m, 3H); 3,95-2,90 (m, 5H); 2,71 (s, 3H); 1,45 and 1,37 (s, 9H); 1,05-2,00 (m, 6H).

25

Reference Example No.11:

4 - [4 - (5 - (R) - hydroxymethyl-2-oxo-oxazolidin-3-yl)phenyl] - piperazin-1-carboxylic acid tert-butyl ester.

30



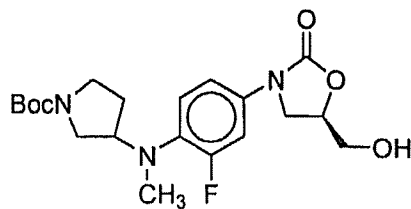
Following a procedure analogous to that of Reference Example No.4 and using 69.2 g (0.169 mol) of the product obtained in Reference Example No.8, 44.4 g (70%) of the product of the title is obtained.

5 ^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42 (d, 2H); 6,92 (d, 2H); 4,80-4,64 (s.c., 1H); 4,02-3,90 (s.c., 3H); 3,80-3,64 (m, 1H); 3,62-3,72 (s.c., 4H); 3,14-3,04 (s.c., 4H); 2,77 (t, 1H, OH); 1.45 (s, 9H).

10 As in the previous preparation, and following the procedure described in Reference Example No.4, the following products are obtained:

Reference Example No.12:

15 3-(R, S)-{[2-fluoro-4-(5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

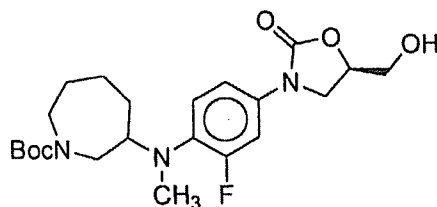


^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,14-7,00 (s.c., 2H); 4,80-4,64 (m, 1H); 4,02-3,64 (s.c., 5H); 3,62-3,40 (s.c., 2H); 3,38-3,18 (s.c., 2H); 2,78 (s.a., 1H, OH); 2,70 (s, 3H); 2,06-1.80 (s.c., 2H); 1.42 (s, 9H).

Reference Example No.13:

3-(R, S)-{[2-fluoro-4-(5-(R)-hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-methyl-amino}-azepan-1-carboxylic acid tert-butyl ester.

5



10

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,95 (m, 1H); 7,40 (dd, 1H); 7,10 (m, 1H); 4,75 (m, 1H); 4,10-3,00 (m, 9H); 2,73 and 2,76 (s, 3H); 1.39 and 1.46 (s, 9H); 1.20-2,00 (m, 6H).

15

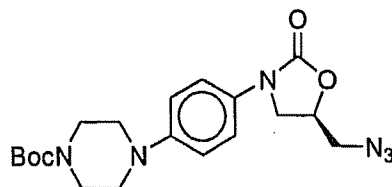
Following the procedure described in method 1 of Reference Example No.5 and using respectively the products obtained in reference examples 11 to 13, the following products are obtained:

20

Reference Example No.14:

4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester.

25



30

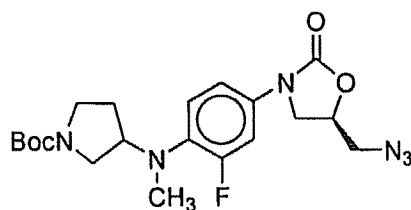
^1H -RMN ($\text{DMSO}-d_6$, 200 MHz, δ (ppm)): 7,44 (d, 2H); 7.02 (d, 2H); 4,96-4,84 (m, 1H); 4,17 (t, 1H); 3,84-3,62 (s.c., 2H); 3,56-3,30 (s.c., 5H); 3,17-3,04 (s.c., 4H); 1.42 (s, 9H).

Reference Example No.15:

3-(R, S)-{[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester.

5

10

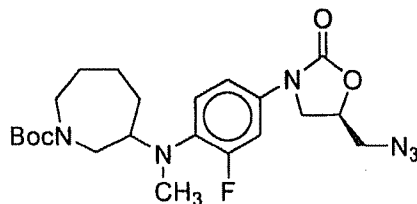


$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H);
7,16-7,01 (s.c., 2H); 4,86-4,72 (m, 1H); 4,06 (t, 1H);
15 3,95-3,40 (s.c., 6H); 3,38-3,17 (s.c., 2H); 2,73 (s, 3H);
2,10-1.73 (s.c., 2H); 1.45 (s, 9H).

Reference Example No.16:

3-(R, S)-{[4-(5(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-methyl-amino}-azepan-1-carboxylic acid tert-butyl ester.

25



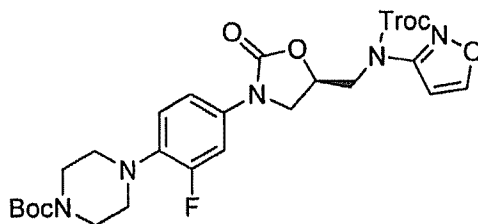
$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (m, 1H);
30 7,20-6,80 (m, 2H); 4,75 (m, 1H); 4,05 (t, 1H); 3,95-3,00
(m, 8H); 2,74 (m, 3H); 2,00-1.00 (m, 6H); 1.46 and 1.39
(s, 9H).

Reference Example No.17:

4-[2-Fluoro-4-(5-(R)-{[isoxazol-3-yl-(2,2,2-trichloroethoxycarbonyl)-amino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester.

5

10



3.4 g (13 mmol) of 3-(2,2,2-trichloroethoxycarbonylamino)-isoxazol (prepared according to WO 0021960) is dissolved in 100 ml of DMF, and 536 mg (14.3 mmol) of sodium hydride (60% paste) is added in portions and stirred for 30 minutes. 6 g (12.7 mmol) of 4-{2-Fluoro-4-[2-oxo-5-(R)-(toluene-4-sulphonyloxymethyl)-oxazolidin-3-yl]-phenyl}-piperazine-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added dissolved in 30 ml of DMF.

The reaction is heated to 90°C for 20 h. It is allowed to cool and is poured onto 500 ml of water. It is extracted with 3x250 ml of a 4/1 mixture of toluene/ethyl acetate. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

Elution with Heptane/Ethyl acetate 7/3 yields 2.530 g of the product of the title.

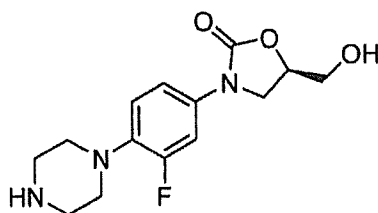
¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,45 (dd, 1H); 7,12 (m, 1H); 6,95 (m, 2H); 5,15 (m, 1H);

4,90 (m, 2H); 4,50 (dd, 1H); 4,25 (dd, 1H); 4,13 (t, 1H);
3,85 (dd, 1H); 3,60 (m, 4H); 3,00 (m, 4H); 1.49 (s, 9H).

Reference Example No.18:

5 3-(3-Fluoro-4-piperazin-1-yl-phenyl)-5-(R)-
 hydroxymethyl-oxazolidin-2-one

10



To 5 g (0.0126 mol) of 4-[2-fluoro-4-(5-(R)-
15 hydroxymethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-
carboxylic acid tert-butyl ester (obtained according to US
5547950) in 100 ml of ethanol is added 2.6 g (0.0139 mol)
of para-toluenesulphonic acid and this is heated to reflux
for 16 h. It is concentrated to dryness and the residue is
20 chromatographed on silica gel (80 g) to the upper part of
which alumina (20 g) is added.

Elution with dichloromethane/ethanol/ammonium
hydroxide (90/10/1%) yields 1.6 g of the product of the
25 title.

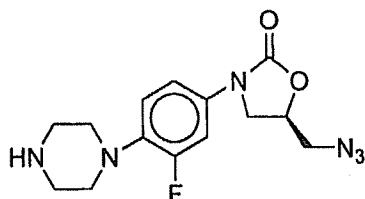
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,50 (d.d., 1H);
7,24-7,00 (s.c, 2H); 4,70 (m, 1H); 4,04 (t, 1H); 3,82-3,42
(s.c, 3H); 2,86 (s.a, 8H).

30

Reference Example No.19:

5-(R)-azidomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.

5



10

To 5 g (0.011 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 100 ml of ethanol is added 2.4 g (0.013 mol) of p-toluenesulphonic acid.

It is heated to reflux for 16 h. Once the reaction has ended it is concentrated to dryness and the residues pass through a column of silica gel (100 g) containing 25 g of alumina in the upper part.

Elution with dichloromethane/ethanol/ammonium hydroxide (80/20/1%) yields 3.5 g of the product of the title.

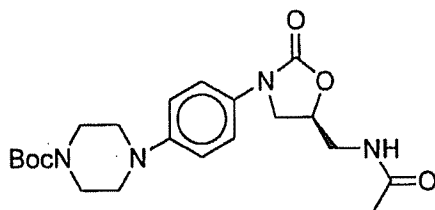
25

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,42 (dd, 1H); 7,10 (dd, 1H); 6,94 (t, 1H); 4,84-4,76 (m, 1H); 4,05 (t, 1H); 3,83-3,50 (s.c, 3H); 3,03 (s, 3H).

Reference Example No.20:

4-{4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl}-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

5



10

To 40 g (0.0668 mol) of the product of Reference Example No.14 in 1,000 ml of ethyl acetate is added 4 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When reduction of the azide group has finished (thin-layer chromatography), it is cooled to 0°C and 8.4 ml (0.103 mol) of pyridine and 13.4 ml (0.103 mol) of acetic anhydride are added.

20

It is stirred at 0°C for 30 min and then for 16 h at room temperature. It is filtered over decalite and the filtration liquids are concentrated to dryness.

25 The residue is chromatographed on silica gel. Elution with dichloromethane/ethanol 95/5 yields 27 g (97%) of the product of the title.

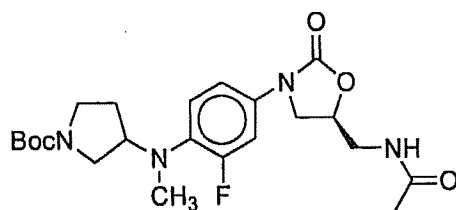
¹H-RMN (DMSO, 200 MHz, δ (ppm)): 8,30 (t, 1H, NH); 7,41 (d, 2H); 7,00 (d, 2H); 4,80-4,60 (m, 1H); 4,10 (t, 1H); 3,72 (t, 1H); 3,55-3,38 (s.c., 6H); 3,15-3,03 (s.c., 4H); 1.83 (s, 3H); 1.42 (s, 9H).

Following the procedure described above and using the products of reference examples No. 15 and No. 16, the following products are obtained:

5 **Reference Example No.21.**

3-(R, S)-({4-5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-methyl-amino)-pyrrolidine-1-carboxylic acid tert-butyl ester.

10



15

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,41 (dd, 1H); 7,10-7,00 (s.c., 2H); 6,61 (t, 1H, NH); 4,82-4,70 (m, 1H); 4,02 (t, 1H); 3,97-3,40 (s.c., 6H); 3,40-3,18 (s.c., 2H); 2,75 (s, 3H); 2,10-1.80 (s.c., 2H); 1.42 (s, 9H).

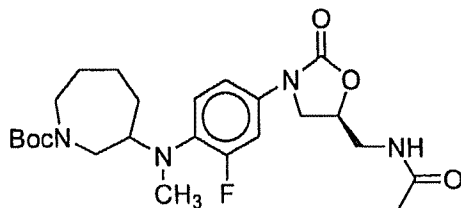
20

Reference Example No.22.

3-(R, S)-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-carboxylic acid tert-butyl ester.

25

30



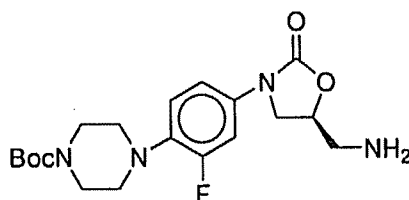
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,15-6,85 (m, 2H); 6,45 (m, 1H); 4,75 (m, 1H); 4,01 (t,

1H); 3,90-3,00 (m, 8H); 2,76 and 2,23 (s, 3H); 2,03 (s, 3H); 1,46 and 1,39 (s, 9H); 2,00-1,10 (m, 6H).

Reference Example No.23.

5 4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-carboxylic tert-butyl ester.

10



To 30 g (0.071 mol) of 4-[4-(5-(R)-azidomethyl-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) in 300 ml of ethanol is added 3 g of 10% Pd/C paste and it is placed under atmosphere of hydrogen at atmospheric pressure and room temperature. When the reaction has finished (thin-layer chromatography eluted with dichloromethane-ethanol 95/5) it is filtered over decalite and the decalite washed with 50 ml of ethanol.

The filtering liquids are concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol/ammonium hydroxide 90/10/1% yields 14 g (50%) of the product of the title.

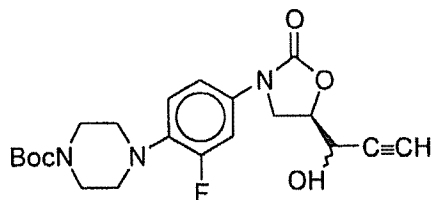
30

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 7,47 (dd, 1H); 7,13 (dd, 1H); 6,94 (t, 1H); 4,75-4,60 (m, 1H); 4,01 (t, 1H); 3,82 (dd, 1H); 3,62-3,51 (s.c., 4H); 3,20-2,90 (s.c., 6H); 1.50 (s, 9H); 1.40 (s.a., 2H, NH₂).

Reference Example No.24.

4-{2-fluoro-4-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-carboxylic acid tert-butyl ester.

5



10

To 2.4 g (32.2 mmol) of tert-butanol in 30 ml of dry tetrahydrofuran, cooled to -10°C, is added 9.2 ml (23 mmol) of n-Buli (2.5 M in hexane).

15 It is stirred for 30 min and allowed to reach a temperature of 0°C. 4.49 g (10 mmol) of 4-(4-benzyloxycarbonylamino-2-fluoro-phenyl)-piperazin-1-carboxylic acid tert-butyl ester (obtained according to US 5547950) is then added, dissolved in 10 ml of dry
20 dimethylformamide.

After stirring for 10 min at 0°C, 3.4 g (12.5 mmol) of 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate (obtained according to EP 1029854 A1) dissolved in 5 ml of DMF is
25 then added dropwise.

It is allowed to reach room temperature and stirred for 16 h. It is poured onto 200 ml of saturated solution of sodium bicarbonate and extracted with 3 x 150 ml of ethyl
30 acetate. The organic extracts are washed with 150 ml of water. The organic phase is dried and concentrated and the residue is chromatographed on silica gel.

Elution with ethyl acetate/heptane 1/1 yields 2.6 g (62%) of the product of the title.

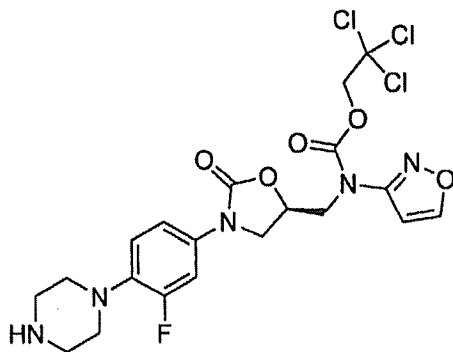
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 7,45 (dd, 1H); 5 7,15 (m, 1H); 6,95 (t, 1H); 4,75 (m, 2H); 4,30-2,90 (m, 3H); 3,60 (m, 4H); 3,00 (m, 4H); 2,53 (d, 1H); 1.48 (s, 9H).

Following the procedure described in reference 10 examples 18 and 19 and using respectively the compounds obtained in reference examples 17 and 20 to 24 the following products are obtained:

Reference Example No.25.

15 [3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-ylmethyl]-isoxazol-3-yl-carbamate of 2,2,2-trichloro-ethyl

20

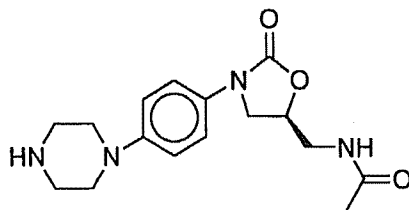


25

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,34 (d, 1H); 7,42 (dd, 1H); 7,10 (dd, 1H); 6,95 (m, 2H); 5,15 (m, 1H); 4,95 (m, 2H); 4,52 (dd, 1H); 4,25 (dd, 1H); 4,12 (t, 1H); 30 3,80 (dd, 1H); 3,12 (m, 8H).

Reference Example No.26.

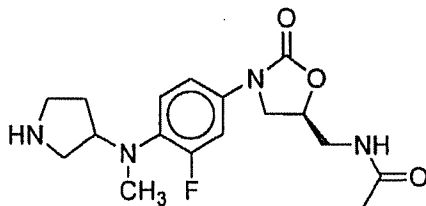
N-[2-oxo-3-(4-piperazin-1-yl-phenyl)-oxazolidin-5-(S)-ylmethyl]acetamide.



^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 8,30 (t, 1H, NH); 7,41 (dd, 2H); 7,00 (dd, 2H); 4,80-4,60 (m, 1H); 4,06 (t, 1H); 3,71 (dd, 1H); 3,42 (t, 2H); 3,30-3,10 (s.c., 8H); 1.82 (s, 3H).

Reference Example No.27.

N-{3(R,S)-[3-fluoro-4-(methyl-pyrrolidine-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.

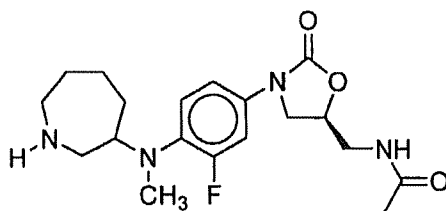


^1H -RMN (CDCl $_3$, 200 MHz, δ (ppm)): 7,39 (dd, 1H); 7,10-6,97 (s.c., 2H); 6,49 (t, 1H, NH); 4,83-4,70 (m, 1H); 4,02 (t, 1H); 3,90-3,60 (s.c., 4H); 3,13-2,80 (s.c., 30 4H); 2,72 (s, 3H); 2,02 (s, 3H); 2,00-1.65 (s.c., 2H).

Reference Example No.28.

N-{3 (R,S) - [4 - (azepan-3-yl-methyl-amino) - 3-fluoro-phenyl] - 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide.

5



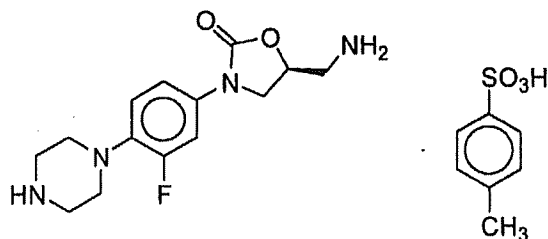
10

$^1\text{H-RMN}$ (CDCl_3 , 200 MHz, δ (ppm)): 7,35 (dd, 1H); 7,05 (m, 1H); 6,90 (t, 1H); 6,75 (t, 1H, NH); 4,75 (m, 1H); 4,00 (t, 1H); 3,90-3,30 (m, 4H); 3,20-2,60 (m, 4H); 2,72 (s, 3H); 2,30 (s.a., 1H); 2,02 (s, 3H); 1.90-1.00 (m, 15 6H).

Reference Example No.29.

p-toluenesulphate of 5-(S)-aminomethyl-3-(3-fluoro-4-piperazin-1-yl-phenyl)-oxazolidin-2-one.

20

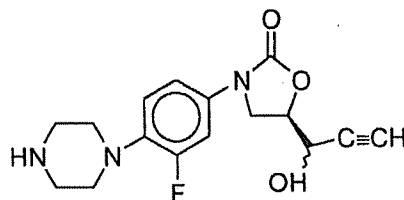


25

$^1\text{H-RMN}$ (DMSO-d_6 , 200 MHz, δ (ppm)): 7,56 (dd, 1H); 7,50 (d, 2H); 7,22-7,06 (s.c., 4H); 4,90-4,74 (m, 1H); 4,14 (t, 1H); 3,84-3,76 (m, 1H); 3,25-3,05 (s.c., 10H); 30 2,26 (s, 3H).

Reference Example No.30.

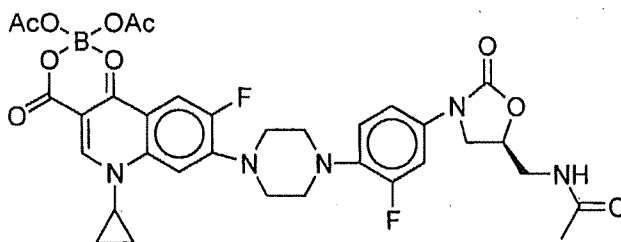
3-(3-fluoro-4-piperazin-1-yl-phenyl)-5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-oxazolidin-2-one.



^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 7,50 (m, 1H); 7,20 (m, 1H); 7,03 (m, 1H); 6,15 (s.a., 1H); 4,70 (m, 1H); 4,52 (m, 1H); 4,10 (t, 1H); 3,85 (m, 1H); 3,25 (m, 1H); 3,23 (s.a., 1H).

Reference Example No.31:

7-(4-{-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid diacethoxyboron
chelate.



To 1 g (3 mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) in 30 ml of acetonitrile are added 1.22 g of 7-chloro-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid diacethoxyboron chelate (obtained according to WO 8807998) and 0.43 ml (3 mmol) of triethylamine.

5 The reaction is heated to reflux for 16 h. It is concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane/ethanol 90/10 yields 0.8 g of 10 the product of the title.

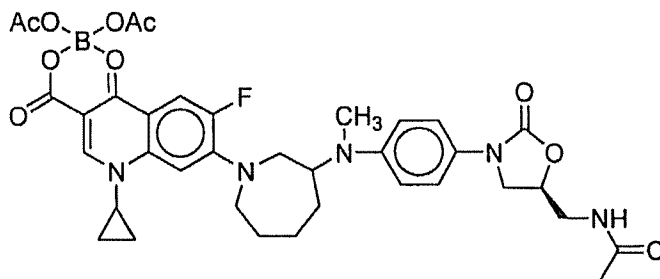
^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 9,04 (s, 1H); 8,10 (d, 1H); 7,56-7,44 (s.c., 2H); 7,08 (dd, 1H); 6,97 (t, 1H); 6,38 (t, 1H, NH); 4,82-4,68 (m, 1H); 4,01 (t, 15 1H); 3,90-3,56 (s.c., 8H); 3,30-3,20 (s.a., 4H); 2,04 (s, 6H); 2,02 (s, 3H); 1.90-1.20 (s.c., 2H).

Reference Example No.32.

7-[3-(R,S)-({4-[5-(S)-(acetylamino-methyl)-2-oxo-
20 oxazolidin-3-yl]-2-fluoro-phenyl}-methylamino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-
carboxylic acid diacethoxyboron chelate.

25

30



Following the procedure of the previous example and using the product obtained in Reference Example No. 28, the product of the title is obtained.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H); 7,90 (d, 1H); 7,60-7,40 (m, 2H); 7,30-7,10 (m, 2H); 4,75 (m, 1H); 4,30-3,40 (m, 10H); 2,80 (s, 3H); 2,10-1.05 (m, 10H); 1.93 (s, 6H); 1.88 (s, 3H).

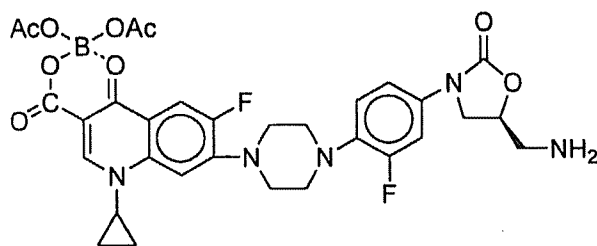
5

Reference Example No.33.

7-{4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-
oxo-1,4-dihydro-quinoline-3-carboxylic acid

10 diacethoxyboron chelate.

15



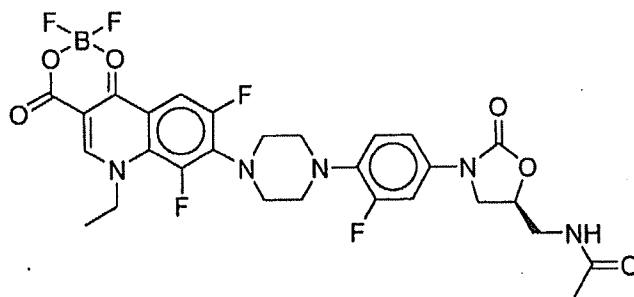
20 Following the procedure described in Reference Example No. 31 and using the product obtained in Reference Example No. 29 and using 2 equivalents of triethylamine instead of only one equivalent, the product of the title is obtained.

25 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,03 (s, 1H); 8,04 (d, 1H); 7,82 (d, 1H); 7,59 (dd, 1H); 7,24 (dd, 1H); 7,17 (t, 1H); 4,70-4,56 (m, 1H); 4,14 (s.a., 1H); 4,08 (t, 1H); 3,84 (dd, 1H); 3,64 (s.a., 4H); 3,23 (s.a., 4H); 2,90-2,70 (s.c., 2H); 2,20 (s.a., 2H, NH_2); 1.90 (s, 6H);
30 1.50-1.20 (s.c., 4H).

Reference Example No.34.

7-(4-{5-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate.

10



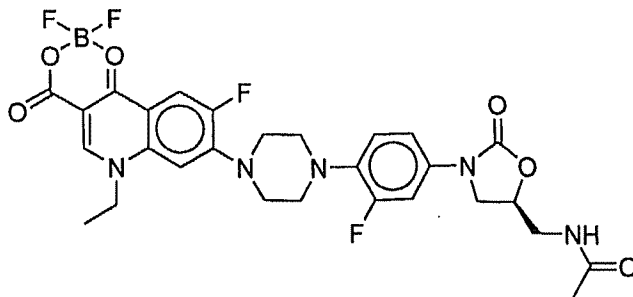
Following a procedure analogous to that described in Reference Example No. 31 and using 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate (obtained according to WO 8807998) the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,44 (s, 1H); 8,27 (t, 1H, NH); 8,09 (d, 1H); 7,54 (dd, 1H); 7,30-7,06 (s.c., 2H); 5,00-4,60 (s.c., 3H); 4,10 (t, 1H); 3,80-2,95 (s.c., 11H); 1.85 (s, 3H); 1.55 (t, 3H).

Reference Example No.35.

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate.

30

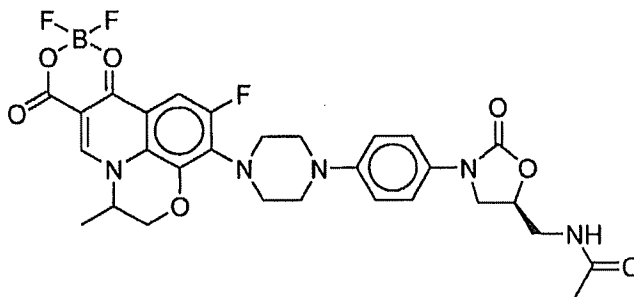


Following a procedure analogous to that described in Reference Example No. 31 and using 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid boron difluoride chelate (obtained according to JP 59122470) the product of the title is obtained.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,42 (s, 1H); 8,30 (t, 1H, NH); 8,17 (d, 1H); 7,60-7,40 (s.c., 2H); 7,25-7,05 (s.c., 2H); 4,90 (c, 2H); 4,80-4,60 (m, 1H); 10 4,14 (t, 1H); 3,80-2,90 (s.c., 11H); 1.84 (s, 3H); 1.52 (t, 3H).

Reference Example No.36.

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3-aza-phenalen-5-carboxylic acid boron difluoride chelate.



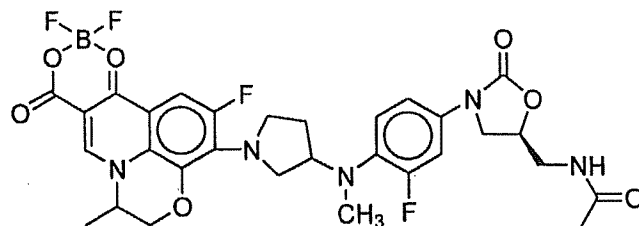
Using 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid boron difluoride chelate (obtained according to JP 58029789) and following a procedure analogous to that described in Reference Example No.31 the product of the title is obtained.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,44 (s, 1H); 25 8,30 (t, 1H, NH); 7,84 (d, 1H); 7,43 (d, 2H); 7,05 (d, 2H); 5,30-5,10 (m, 1H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,15 (s.c., 11H); 1.84 (s, 3H); 1.58 (d, 3H).

Reference Example No.37.

9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluorophenyl}-methyl-amino)-pyrrolidone-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
5 phenalen-5-carboxylic acid boron difluoride chelate.

10



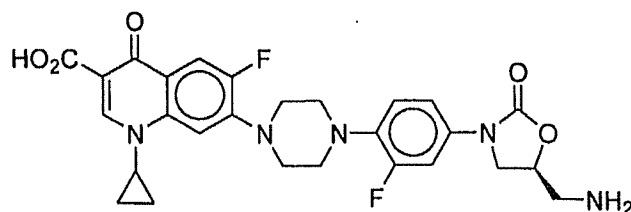
In a manner analogous to the previous example and using
 15 the compound obtained in Reference Example No.27 the
 product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,36 (s, 1H);
 8,25 (t, 1H, NH); 7,74 (d, 1H); 7,50 (dd, 1H); 7,30-7,10
 20 (s.c., 2H); 5,20-3,00 (s.c., 13H); 2,78 (s, 3H); 1.82 (s,
 3H); 2,20-1.80 (s.c., 2H); 1.50 (d, 3H).

Reference Example No.38.

4-{4-[4(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-
 25 phenyl]-piperazin-1-yl}-1-cyclopropyl-6-fluoro-4-oxo-1,4-
dihydro-quinoline-3-carboxylic acid.

30



Method 1:

To 13.3 g (0.02 mol) of the product obtained in Reference
5 Example No.33 in 300 ml of acetonitrile and 300 ml of
water is added 96 ml (0.096 mol) of sodium hydroxide 1N.

It is stirred at room temperature for 2 h. The
acetonitrile is concentrated in a rotovapor and to the
10 resulting aqueous solution is added 96 ml of hydrochloric
acid 1 N.

The precipitate formed is filtered to yield 2.8 g. The
filtering liquids are extracted with 4 x 200 ml of
15 dichloromethane/ethanol 90/10. The extracts are dried and
and concentrated, thus yielding a further 6.8 g of the
product of the title.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,70 (s, 1H);
20 7,95 (d, 1H); 7,63 (d, 1H); 7,58 (dd, 1H); 7,26-7,10
(s.c., 2H); 4,80-4,60 (m, 1H); 4,08 (t, 1H); 3,96-3,80
(s.c., 2H); 3,50 (s.a., 4H + NH_2); 3,23 (s.a., 4H); 3,00-
2,80 (s.c., 2H); 1.42-1.15 (s.c., 4H).

25 *Method 2:*

To 40 mg of the product obtained by method 1 of Reference
Example No.5, dissolved in 10 ml of ethanol, is added 0.10
mg of 10% Pd/C paste, and it is placed under atmosphere of
30 hydrogen at atmospheric pressure and room temperature. When
the reaction finishes it is filtered over decalite, which
is washed with 2 x 10 ml of ethanol.

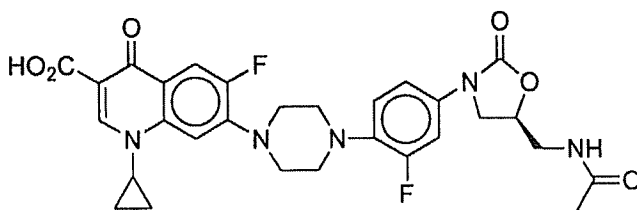
The filtering liquids are concentrated to dryness and thus yield 20 mg of a product identical to that obtained by method 1.

5 COMPOUNDS OF GENERAL FORMULA (I)

Example 1:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-
10 fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

15



To 0.8 g (1.13 mol) of the product of Reference Example No.31 in 20 ml of water and 20 ml of acetonitrile is added 5.6 ml of sodium hydroxyde 1N, and it is stirred at room
20 temperature for 1 h.

The acetonitrile is concentrated and the aqueous phase is acidified with 5.6 ml of hydrochloric acid 1N.

It is extracted with 3 x 50 ml of dichloromethane/ethanol 9/1.

25

The organic phase is dried and concentrated. The residue is stirred for 10 min with 2-propanol and the precipitated solid is filtered. Thus are obtained 290 mg of the product of the title.

30

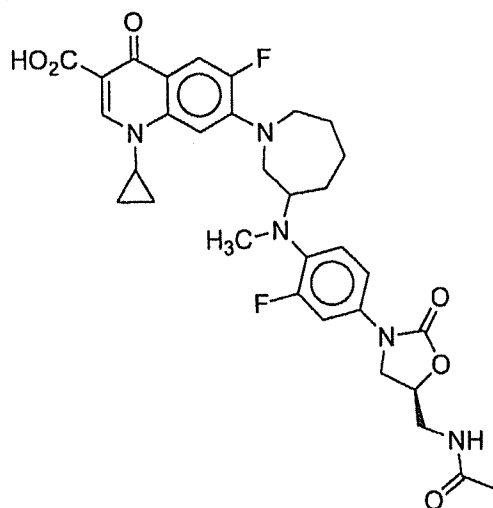
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,72 (s, 1H); 8,33 (t, 1H, NH); 7,99 (d, 1H); 7,64 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,84-4,64 (m, 1H); 4,16 (t, 1H); 3,90-2,90 (s.c., 12H); 1.90 (s, 3H); 1.44-1.16 (s.c., 4H).

Example 2:

7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

10

15



It is obtained by following the procedure of Example 1 and using the product obtained in Reference Example No.32.

20

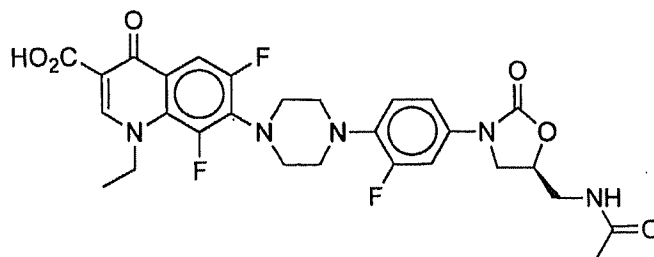
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d, 1H); 7,50 (dd, 1H); 7,30 (d, 1H); 7,25-7,05 (s.c., 2H); 4,75 (m, 1H); 4,20-3,20 (m, 10H); 2,76 (s, 3H); 2,20-1,00 (m, 10H); 1.86 (s, 3H).

25

Example 3:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

30



To 1.9 g (3mmol) of the product obtained in Reference Example No.34 in 100 ml of ethanol and 2.5 ml of water is added 10 ml of triethylamine, and it is heated to reflux 5 for 16 h.

The precipitated salts are filtered. The filtering liquids are concentrated to dryness and the residue is treated with 50 ml of water and the pH adjusted to 5 by addition 10 of hydrochloric acid 1N.

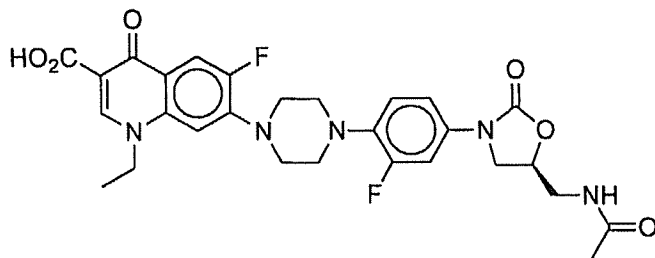
It is extracted with 3 x 75 ml of dichloromethane/ethanol 9/1. The organic phase is dried and concentrated. Thus are obtained 1.2 g of a white solid.

15 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,94 (s, 1H); 8,30 (t, 1H, NH); 7,87 (d, 1H); 7,50 (dd, 1H); 7,25-7,02 (s.c., 2H); 4,80-4,30 (s.c., 3H); 4,10 (t, 1H); 3,80-3,20 (s.c., 7H); 3,10 (s.a., 4H); 1,82 (s, 3H); 1,42 (t, 3H).

20 Example 4:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

25



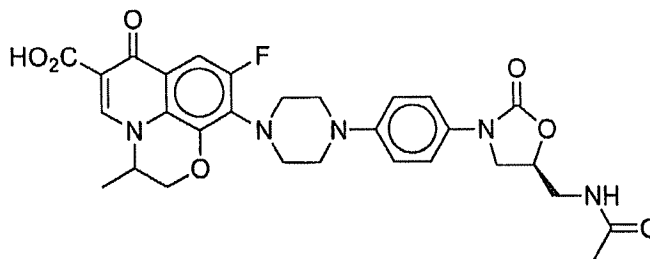
30

Following the procedure of the previous example and using the product obtained in Reference Example No.35 the product of the title is achieved.

5 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,99 (s, 1H); 8,30 (t, 1H, NH); 7,96 (d, 1H); 7,54 (d, 1H); 7,20-7,05 (s.c., 3H); 5,00-4,56 (s.c., 3H); 4,14 (t, 1H); 3,90-3,10 (s.c., 11H); 1.82 (s, 3H); 1,60-1,35 (s.a., 3H).

10 **Example 5:**

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid



15

Following the procedure described in Example 3 and using the product obtained in Reference Example No.36 the product of the title is achieved.

20 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 9,00 (s, 1H); 8,26 (t, 1H, NH); 7,62 (d, 1H); 7,41 (d, 2H); 7,02 (d, 2H); 5,05-4,90 (m, 1H); 4,80-4,75 (s.c., 2H); 4,41 (d, 1H); 4,10 (t, 1H); 3,80-3,00 (s.c., 11H); 1.84 (s, 3H); 1.46 (d, 3H).

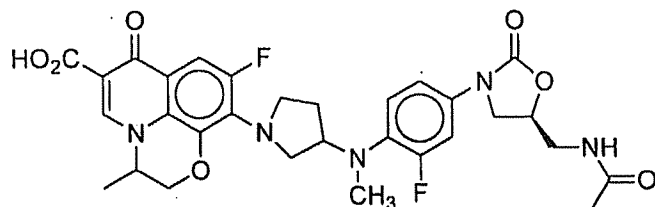
25

Example 6:

9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-

fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid

5



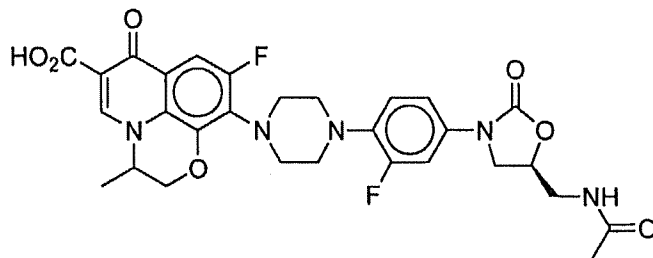
10 Following the procedure of Example No.3 and using the product of Reference Example No.37 the product of the title is obtained.

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,92 (s, 1H); 15 8,30 (t, 1H, NH); 7,60-7,40 (s.c., 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,80-4,45 (s.c., 3H); 4,40-4,20 (s.c., 1H); 4,10 (t, 1H), 4,02-3,20 (s.c., 7H); 2,70 (s, 3H); 2,20-1,90 (s.c., 2H); 1,84 (s, 3H); 1,45 (s.a., 3H).

20 Example 7:

9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

25



30

To 1.6 g (5mmol) of 8,9-difluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate and 1.7 g (5mmol) of N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-

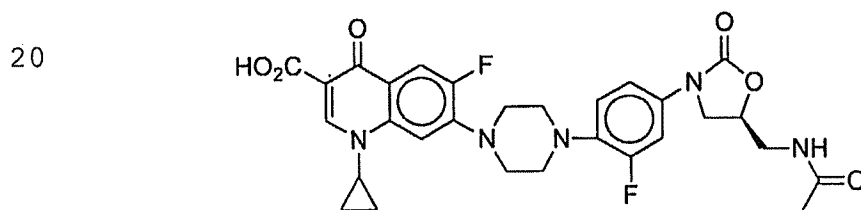
acetamide (obtained according to US 5547950) in 50 ml of N-methyl-pyrrolidin-2-one is added 0.7 ml (5mmol) of triethylamine and it is heated at 110°C for 16 h.

5 The solvent is distilled under vacuum and the residue is stirred for 30 min with dichloromethane/ethanol, precipitating a solid which is filtered and yields 1.2 g (40%) of pure product.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 9,00 (s, 1H); 10 8,25 (t, 1H, NH); 7,62 (d, 1H); 7,52 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,99 (m, 1H); 4,80-4,60 (m, 1H); 4,62 (d, 1H); 4,40 (d, 1H); 4,10 (t, 1H); 3,80-3,60 (m, 1H); 3,60-2,80 (s.c., 10H); 1,84 (s, 3H); 1,50 (d, 3H).

15 Example 8:

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

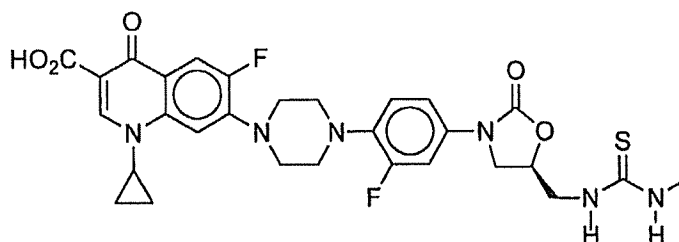


25 To 6 g (0.011 mol) of the product of Reference Example No.38 in 100 ml of pyridine is added 2.8 ml (0.022 mol) of acetic anhydride. It is heated at 50°C for 2 h. The pyridine is concentrated to dryness and to the residue is added 200 ml of water and it is stirred for 5 min. The
30 precipitated solid is filtered and dissolved in dichloromethane and chromatographed on silica gel. Elution with dichloromethane-ethanol 90/10 yields 4 g (63%) of pure product identical to that obtained in Example 1.

Example 9:

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

10



To 0.81 g (1.5 mmol) of the product of Reference Example No.38 in 10 ml of pyridine is added 0.22 g (3 mmol) of methylisothiocyanate. It is heated at 60°C for 10 minutes. It is concentrated to dryness and the residue is stirred for 20 min with 30 ml of water. The precipitated solid is filtered and 0.5 g of pure product is obtained.

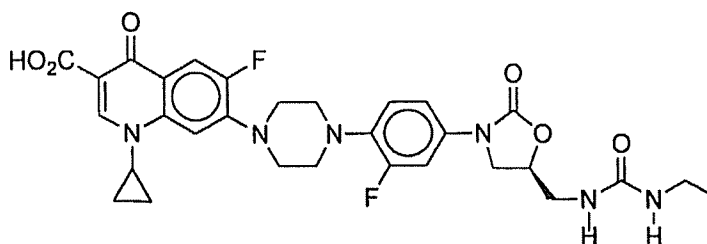
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,82 (t, 1H, NH); 7,80-7,50 (s.a., 1H, NH); 7,64 (d, 1H); 7,56 (dd, 1H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,40 (s.a., 4H); 3,30-3,10 (s.a., 4H); 2,82 (s.a., 3H); 1,44 -1,16 (s.c., 4H).

25

Example 10:

1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

30



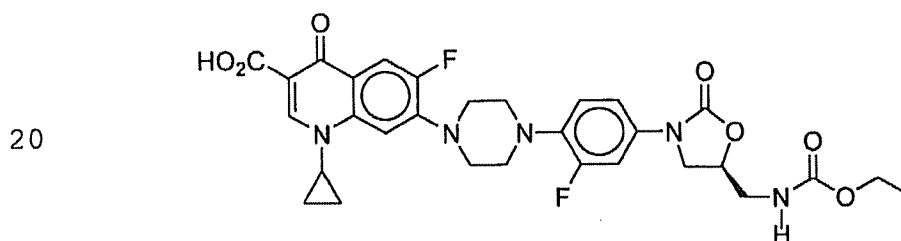
In a similar way to the previous Example and replacing the methylisothiocyanate by ethylisocyanate the product of the title is obtained.

5

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,96 (d, 1H); 7,66 (d, 1H); 7,58 (dd, 1H); 7,30-7,10 (s.c., 1H); 6,22 (t, 1H, NH); 5,99 (t, 1H, NH); 4,80-4,64 (s.c., 1H); 4,10 (t, 1H); 3,90-3,78 (m, 1H); 3,72 (dd, 10 1H); 3,60-3,20 (s.c., 10H); 3,10-2,90 (s.c., 2H); 1.44-1.10 (s.c., 4H); 0.98 (t, 3H).

Example 11:

1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-
15 2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



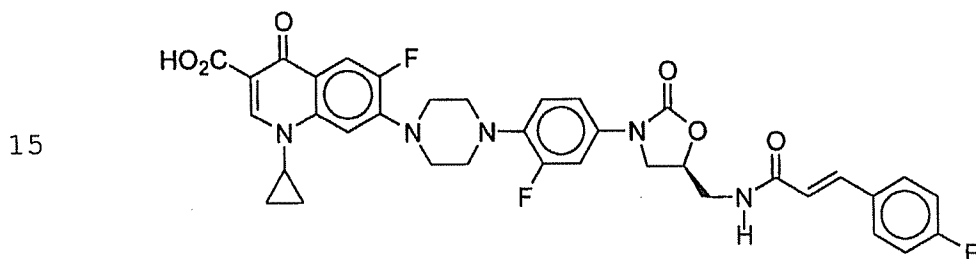
To 0.81 g of the product of Reference Example 25 No.38 in 20 ml of tetrahydrofuran are added 0.25 g of sodium bicarbonate and 0.3 g of ethyl chloroformate.

It is heated to reflux for 16 h. It is concentrated to dryness and the residue is treated with 30 ml of water and extracted with 3 x 50 ml of dichloromethane-ethanol 90/10. The organic phase is dried and concentrated to a volume of 20 ml. The precipitated solid is filtered and 0.3 g of pure product is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 7,98 (d, 1H); 7,64 (d, 1H); 7,56 (dd, 1H); 7,50 (t, 1H, NH); 7,30-7,10 (s.c., 2H); 4,80-4,64 (m, 1H); 4,14 (t, 1H); 4,02 (c, 2H); 3,96-3,70 (s.c., 2H); 3,60-3,10 (s.c., 5 10H); 1.42-1.10 (s.c., 4H); 1.17 (t, 3H).

Example 12:

1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



To 0.6 g (1.1 mmol) of the product of Reference 20 Example No.38 in 20 ml of dry dichloromethane are added 0.17 ml (1.22 mmol) of triethylamine and 0.3 g (1.33 mmol) of 4-fluorocinnamoyl chloride.

The reaction is maintained at room temperature for 25 16 h, then concentrated to dryness and the residue is chromatographed on silica gel.

Elution with dichloromethane-ethanol 95/5 yields 0.3 g of pure product.

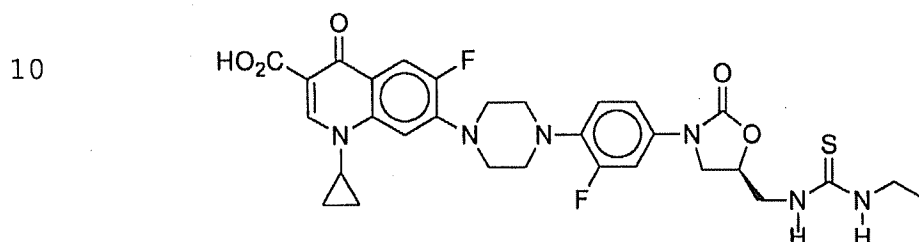
30

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H); 8,58 (t, 1H, NH); 7,96 (d, 1H); 7,70-7,58 (s.c., 4H); 7,44 (d, 1H); 7,30-7,10 (s.c., 4H); 6,64 (d, 1H); 4,90-4,76 (m,

1H); 4,16 (t, 1H); 3,92-3,70 (s.c., 2H); 3,64-3,10 (s.c., 10H); 1.42-1.10 (s.c., 4H).

Example 13:

5 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluorophenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

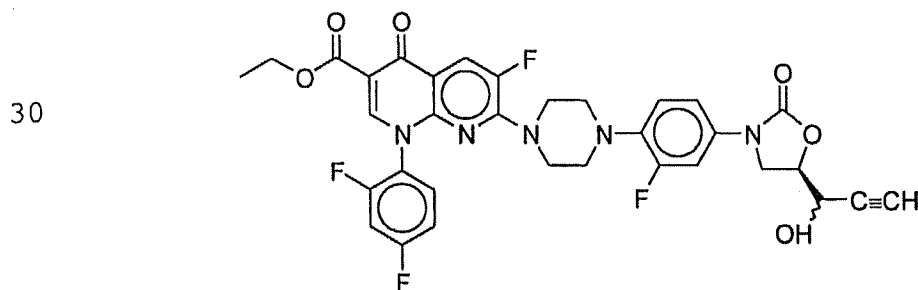


15 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by ethylisothiocyanate, the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 8,70 (s, 1H); 7,98-7,50 (m, 4H,); 7,30-7,10 (s.c., 20 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.44 -1.16 (s.c., 4H).; 1.02 (t., 3H).

Example 14

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-
25 (1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester



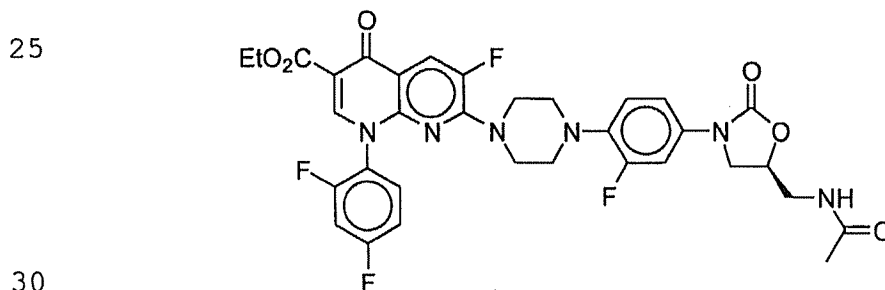
To 0.32 g (1 mmol) of the product of Reference Example No.30 in 10 ml of pyridine are added 0.42 g (1mmol) of 7-chloro-1-(2,4-difluorophenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester (ACROS) and 0.28 ml of triethylamine. The reaction is maintained at room temperature for 48 h. It is concentrated to dryness and the residue is chromatographed on silica gel.

10 Elution with dichloromethane/ethanol/ammonium hydroxide 95/5/1% yields 0.436 g (66%) of the product of the title.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,42 (s, 1H);
15 8,15 (d, 1H); 7,40 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H);
4,75 (m, 1H); 4,70 (m, 1H); 4,38 (c, 2H); 4,10 (m, 2H);
3,70 (m, 4H); 3,04 (m, 4H); 2,50 (m, 1H); 1.40 (t, 3H).

Example 15

20 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester.



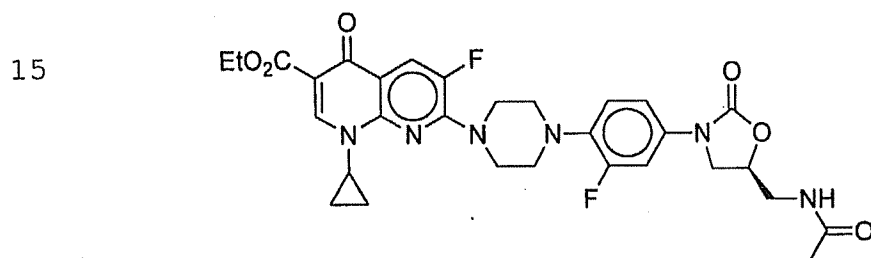
Following the procedure of the previous example and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-

oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 7,42 (dd, 1H); 7,16-6,80 (s.c., 5H); 6,41 5 (t, 1H, NH); 4,84-4,70 (m, 1H); 4,39 (c, 2H); 4,02 (t, 1H); 4,80-4,60 (s.c., 7H); 3,10-2,95 (s.a., 4H); 2,02 (s, 3H); 1.40 (t, 3H).

Example 16

10 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester



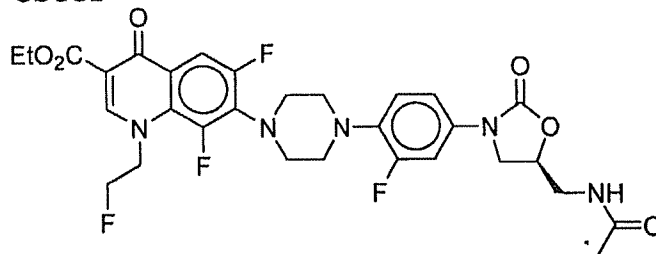
20 Following the procedure described in example 14 and using N-[3-(3-Fluoro-4-piperazin-1-yl-phenyl)-2-oxo-oxazolidin-5-(S)-ylmethyl]-acetamide (obtained according to US 5547950) and 7-chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester (EP 0187376B1) the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,52 (s, 1H); 8,11 (d, 1H); 7,48 (dd, 1H); 7,08 (m, 1H); 6,94 (t, 1H); 6,74 (t, 1H, NH); 4,79 (m, 1H); 4,37 (c, 2H); 4,01 (m, 30 5H); 3,76 (m, 1H); 3,66 (m, 2H); 3,53 (m, 1H); 3,20 (m, 4H); 2,04 (s, 3H); 1.40 (t, 3H); 1.23 (m, 2H); 1.05 (m, 2H).

Example 17

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

10

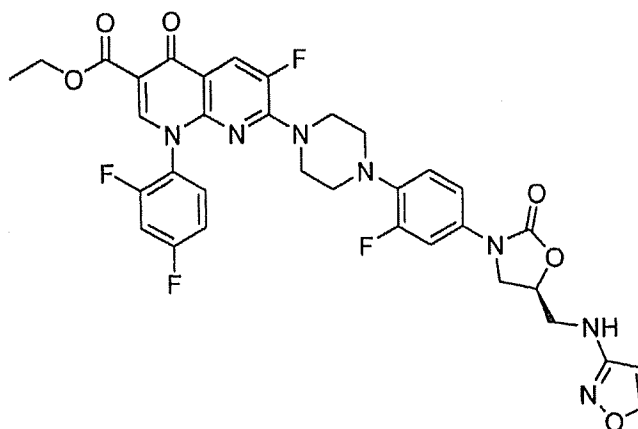


Following a procedure analogous to the previous ones and replacing the derivative of naphthyridine by 6,7,8-trifluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester, the product of the title is obtained.

^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 8,59 (s, 1H); 8,30 (t, 1H, NH); 7,79 (d, 1H); 7,50 (d, 1H); 7,30-7,00 (s.c., 2H); 5,05-4,60 (s.c., 5H); 4,21 (c, 2H); 4,15 (t, 1H); 3,80-3,00 (s.c., 11H); 1.82 (s, 3H); 1.27 (t, 3H).

Example 18

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester.



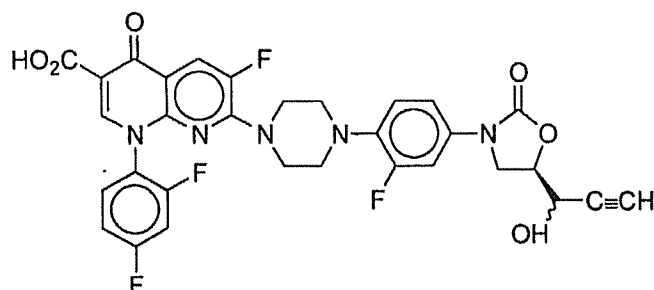
Following the procedure of example 14 and replacing the product of Reference Example No.30 by the product of Reference Example No.25 1-(2,4-difluoro-5 phenyl)-6-fluoro-7-{4-[2-fluoro-4-(5-(R)-{[isoxazol-3-yl-(2,2,2-trichloro-ethoxycarbonyl)-amino]-methyl})-2-oxo-oxazolidin-3-yl]-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester is obtained. To 500 mg thereof, dissolved in 10 ml of tetrahydrofuran is added 5 ml of water, 5 ml of glacial acetic acid and 700 mg of powdered zinc. After stirring for 3 h at room temperature it is filtered over decalite and the filtering liquids concentrated and chromatographed on silica gel. Elution with dichloromethane/ethanol/ammonium hydroxide 98/2/02% yields 247 mg of the product of the title.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,41 (s, 1H); 8,15 (d, 1H); 8,07 (d, 1H); 7,45 (m, 2H); 7,05 (m, 3H); 6,85 (t, 1H); 5,85 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 4,38 (c, 2H); 4,05 (t, 1H); 3,80 (m, 2H); 3,68 (m, 4H); 3,03 (m, 4H); 1.39 (t, 3H).

Example 19

1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-5 carboxylic acid

10



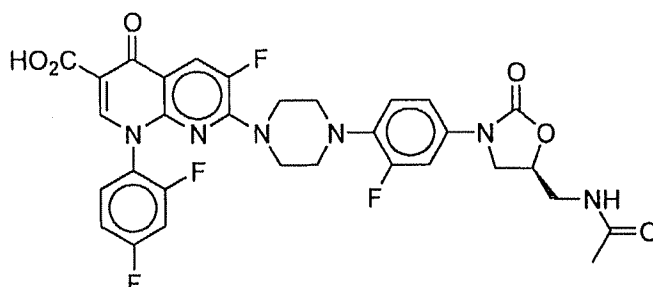
To 0.436 g (0.6 mmol) of the product of example 14 in 5 ml of ethanol and 5 ml of water is added 1.32 ml of sodium hydroxyde 1N. It is heated at 50°C for 3 h. 1.32 ml of HCl 1N is added and it is concentrated to dryness. The residue is chromatographed on silica gel. Elution with dichloromethane/ethanol/acetic acid 95/5/0.5% yields 0.287 g (75%) of the product of the title.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,68 (s, 1H); 8,15 (d, 1H); 7,60-7,27 (m, 2H); 7,20-7,00 (m, 3H); 6,90 (t, 1H); 4,75 (m, 1H); 4,30-4,00 (m, 2H); 3,80 (m, 4H); 3,28 (dd, 1H); 3,20 (m, 1H); 2,50 (d, 1H).

Example 20

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

5



10 Following the procedure described in the previous example and using the product described in Example No.15 the product of the title is obtained.

^1H -RMN (DMSO- d_6 , 200 MHz, δ (ppm)): 8,90 (s, 1H),
 15 8,27 (t, 1H); 8,22 (d, 1H); 7,95-7,80 (m, 1H); 7,80-7,60 (m, 1H); 7,50 (d, 1H); 7,45-7,30 (m, 1H); 7,25-7,00 (s.c., 2H); 4,80-4,62 (m, 1H); 4,12 (t, 1H); 3,80-2,95 (s.c., 11H); 1.84 (s, 3H).

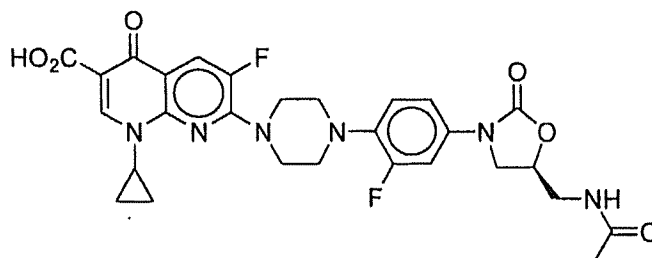
20

Example 21

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid

25

30

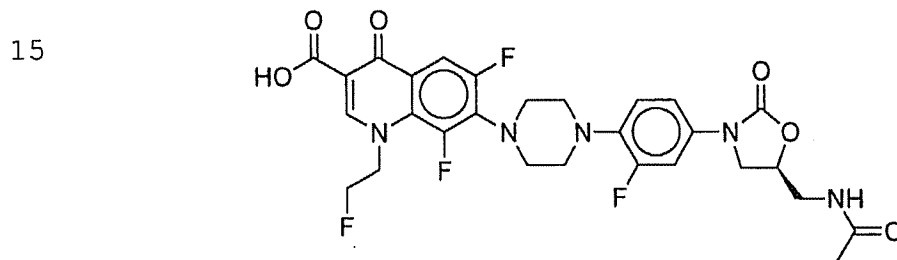


From the product of Example No.16 and following the procedure described above the product of the title is obtained.

¹H-RMN (CDCl₃, 200 MHz, δ (ppm)): 8,74 (s, 1H); 8,12 (m, 1H); 8,10 (d, 1H); 7,50 (m, 1H); 7,12 (m, 1H); 6,95 (t, 1H); 4,79 (m, 1H); 4,10 (m, 4H); 4,05 (m, 1H); 3,89 (m, 1H); 3,67 (m, 1H); 3,58 (m, 2H); 3,24 (m, 4H); 2,00 (s, 3H); 1.30 (m, 2H); 1.15 (m, 2H).

Example 22

7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid



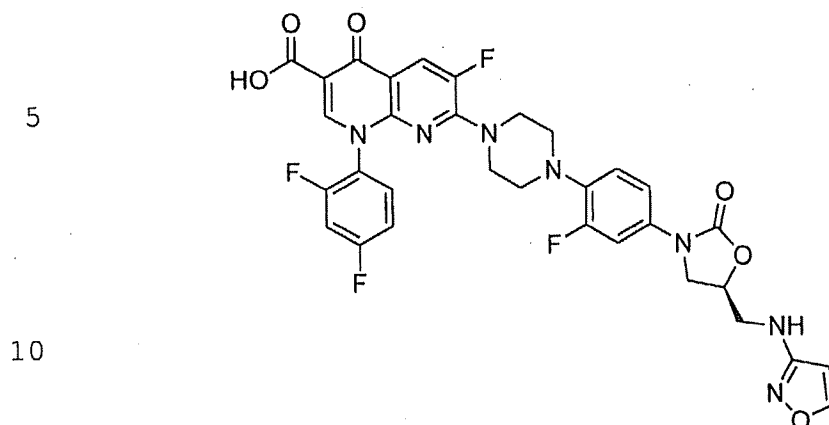
From the product of Example No.17 and following the procedure described in Example No.19, the product of the title is obtained.

25 ¹H-RMN (DMSO-d₆, 200 MHz, δ (ppm)): 8,84 (s, 1H); 8,26 (t, 1H, NH); 7,92 (d, 1H); 7,56 (d, 1H); 7,35 -7,05 (s.c., 2H); 5,16-4,64 (s.c., 5H); 4,12 (t, 1H); 3,80-3,00 (s.c., 11H); 1.82 (s, 3H).

30 Example 23

1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid

35



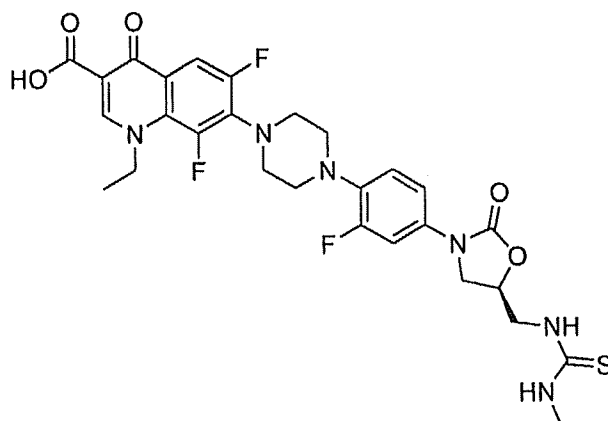
From the product of Example No.18 and following procedure described in Example No.19, the product of the title is 15 obtained.

^1H -RMN (CDCl_3 , 200 MHz, δ (ppm)): 8,69 (s, 1H); 8,15 (d, 1H); 8,06 (d, 1H); 7,45 (m, 2H); 7,10 (m, 3H); 6,90 (t, 1H); 5,90 (s, 1H); 4,95 (m, 1H); 4,50 (m, 1H); 20 4,06 (t, 1H); 4,00-3,50 (m, 6H); 3,05 (m, 4H).

Example 24

1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid

25



To 2 g (6,7 mmol) of 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester in 5 40 ml of N-methyl-2-pyrrolidone are added 3.1 g (6.7 mmol) of the product of Reference Example No.33 and 1.85 ml of triethylamine. The reaction is heated at 100°C for 48 h.

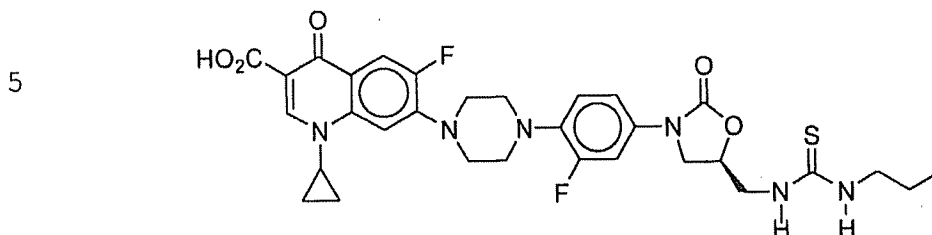
The solvent is distilled under vacuum and the residue is 10 chromatographed on silica gel. Elution with dichloromethane/ethanol 90/10 yields 7-{4-[4-(5-(S)-aminomethyl-2-oxo-oxazolidin-3-yl)-2-fluoro-phenyl]-piperazin-1-yl}-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester. From said product 15 and by following procedure described in Example No.19, the product of the title is obtained.

IR: 3380 cm^{-1} 1750 cm^{-1} 1620 cm^{-1} 1510 cm^{-1}

20

Example 25

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic 25 acid



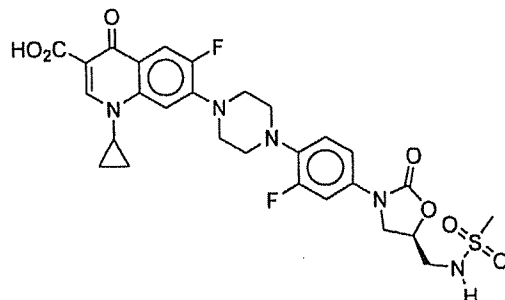
10 Following the procedure described in Example No. 9,
 replacing the methylisothiocyanate by
 propylisothiocyanate, the product of the title is
 obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,70 (s, 1H);
 15 7,92 (d., 1H), 7,90-7,70 (m, 2H, NH); 7,70-7,50 (m., 2H);
 7,30-7,10 (m., 2H); 4,95-4,80 (m, 1H); 4,16 (t, 1H); 4,00-
 3,70 (s.a., 4H); 3,60-3,10 (m., 10H); 1.60 -1.16 (s.c.,
 6H).; 0.84 (t., 3H).

20 **Example 26**

1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-
 (methanesulfonylamino-methyl)-2-oxo oxazolidin-3-yl]-
 phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-quinoline-3-
 25 carboxylic acid

5



10 Following the procedure described in Example No. 9,
 replacing the methyliothiocyanate by
 methanesulphonylchloride, the product of the title is
 obtained.

15 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 15,00 (s.a.,
 1H); 8,70 (s, 1H); 7,96 (d., 1H), 7,76-7,42 (m, 3H); 7,30-
 7,10 (m., 2H); 4,90-4,76 (m, 1H); 4,18 (t, 1H); 4,00-3,20
 (m., 12H); 2,98 (s, 3H); 1.44 -1.16 (m., 4H).

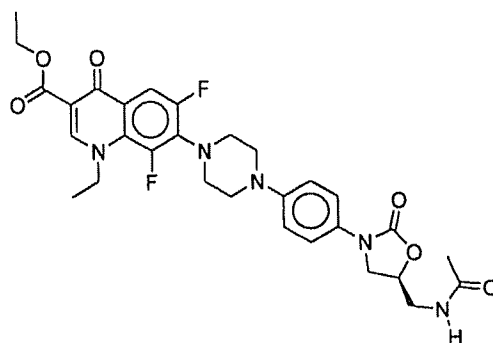
20

Example 27

7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-
 yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-
 dihydro-quinoline-3-carboxylic acid ethyl ester

25

30



Following the procedure described in Example No. 14, using the product obtained in Reference Example No. 26 and 1-ethyl-6,7,8-trifluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester (obtained by esterification of the corresponding acid, described in GB 2057440).

^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8,62 (s, 1H); 8,30 (t, 1H, NH); 7,80 (d., 1H), 7,42 (d, 2H); 7,04 (d., 10 2H); 4,84-4,64 (m, 1H); 4,60-4,40 (s.a., 2H); 4,26 (c, 2H); 4,16 (t, 1H); 3,78 (t, 1H); 3,60-3,20 (m., 10H); 1.90 (s, 3H); 1.44 (t, 3H); 1.30 (t., 3H).

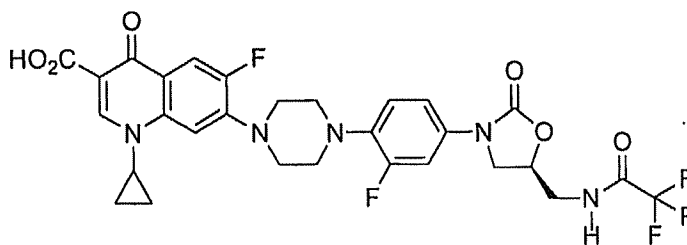
Example 28

15

1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetyl-amino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.

20

25

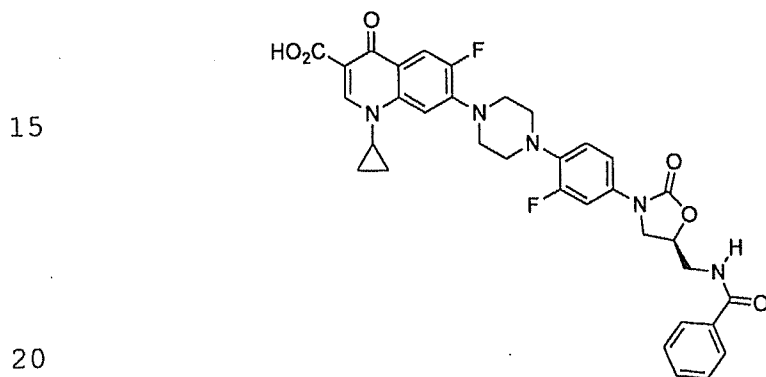


30 Following the procedure described in Example No. 9, replacing the methylisothiocyanate by trifluoroacetic anhydride, the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,06 (s.a., 1H); 9,92 (s.a., 1H, NH); 8,70 (s, 1H); 7,95 (d, 1H,); 7,70-7,50 (m, 2H); 7,30-7,10 (s.c., 2H); 4,95-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,80 (s.a., 2H); 3,60-3,20 (m., 5 10H); 1.44 -1.16 (m., 4H).

Example 29

7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid.



Following the procedure described in Example No. 9, replacing the methylisothiocyanate by benzoyl chloride, the product of the title is obtained.

25

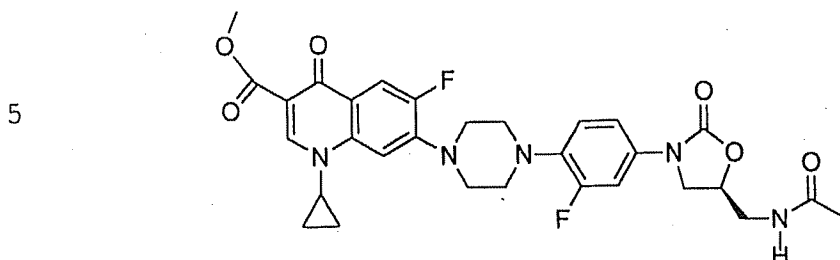
¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 15,20 (s.a., 1H); 8,90 (t, 1H, NH); 8,70 (s, 1H); 8,00-7,85 (m., 3H), 7,76-7,42 (m, 5H); 7,30-7,10 (m., 2H); 4,96-4,80 (m, 1H); 4,20 (t, 1H); 4,00-3,20 (m., 12H); 1.44 -1.16 (m., 4H).

30

Example 30

7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-

fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
methyl ester.



To 1 g (1.7 mmol) of the product of Example 1 in 30 ml of
10 methanol cooled to 0°C is added dropwise 0.37 ml (5.2
mmol) of thionyl chloride. When the addition is finished
it is heated to reflux for 48 hours. It is concentrated to
dryness and the residue is chromatographed on silica gel.
Elution with dichloromethane/methanol/acetic acid 90/10/1
15 yields the product of the title as hydrochloride.

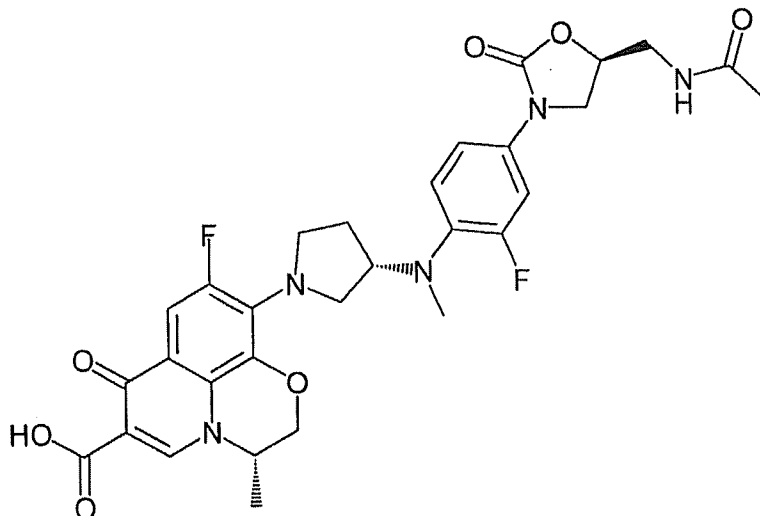
The product thus obtained is dissolved in
dichloromethane/methanol 90/10 and washed with saturated
solution of sodium bicarbonate. The organic phase is dried
20 and concentrated to yield the product of the title in the
form of free base.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8,50 (s, 1H);
8,25 (s.a., 1H, NH); 7,92 (d., 1H), 7,64-7,50 (m, 2H);
25 7,30-7,10 (m., 2H); 4,90-4,70 (m, 1H); 4,16 (t, 1H); 3,90-
3,60 (m., 5H); 3,60-3,20 (m., 10H); 1.86 (s., 1H); 1.45 -
1.10 (m., 4H).

EXAMPLE 31

30

9-[3-(S)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-
oxazolidin-3-yl]-2-fluoro-phenyl)-methyl-amino)-
pyrrolidin-1-yl]-8-fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-
6H-1-oxa-3a-aza-phenalene-5-carboxylic acid.



Following the procedure described in Example 3 and starting
 5 with the corresponding chelate obtained by reaction of N-
 {3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-
 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained
 following the procedure for the obtention of Reference
 Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-
 10 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-
 2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid
 boron difluoride chelate the product of the title is
 obtained.

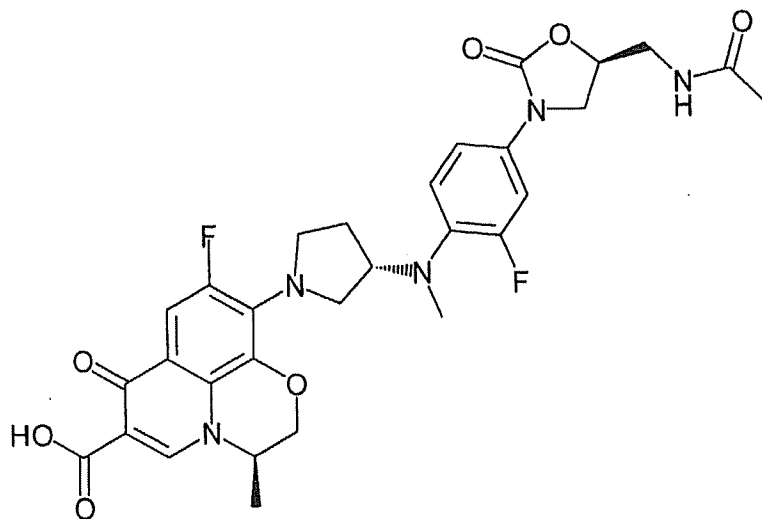
15 $^1\text{H-RMN}$ (DSMO- d_6 , 200 MHz, δ (ppm)): 8.92 (s, 1H);
 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.30-7.10 (m, 2H);
 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.52 (d, 1H); 4.30
 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H);
 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

20

$[\alpha]^{25}_{\text{D}} = -34^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

EXAMPLE 32

9-[3-(S)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-5 fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid



Following the procedure described in Example 3 and starting
 10 with the corresponding chelate obtained by reaction of N-{3-(S)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-
 15 (S)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), **35** (5), 1896-1902) the product of the title is obtained.

20

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.24

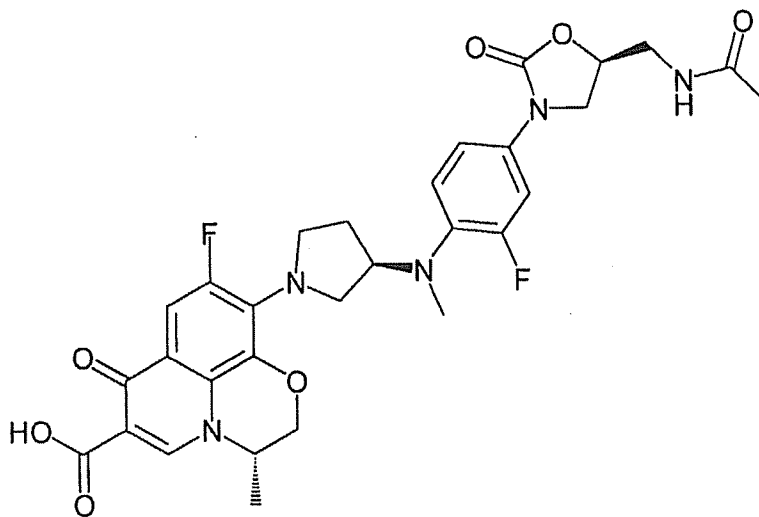
(d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.74 (s, 3H);
2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_D = +66.4^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

5

EXAMPLE 33

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-
10 3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-
fluoro-3-(S)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
phenalene-5-carboxylic acid



15

Following the procedure described in Example 3 and starting
with the corresponding chelate obtained by reaction of N-
{3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-
20 2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained
following the procedure for the obtention of Reference
Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-
(R)-aminopyrrolidine) and 8,9-Difluoro-3-(S)-methyl-6-oxo-

2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate the product of the title is obtained.

5 ^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8.92 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.56 (d, 1H); 4.26 (d, 1H); 4.10 (t, 1H), 4.02-3.30 (m, 8H); 2.76 (s, 3H); 2.20-1.80 (m, 2H); 1.82 (s, 3H); 1.40 (d, 3H)..

10

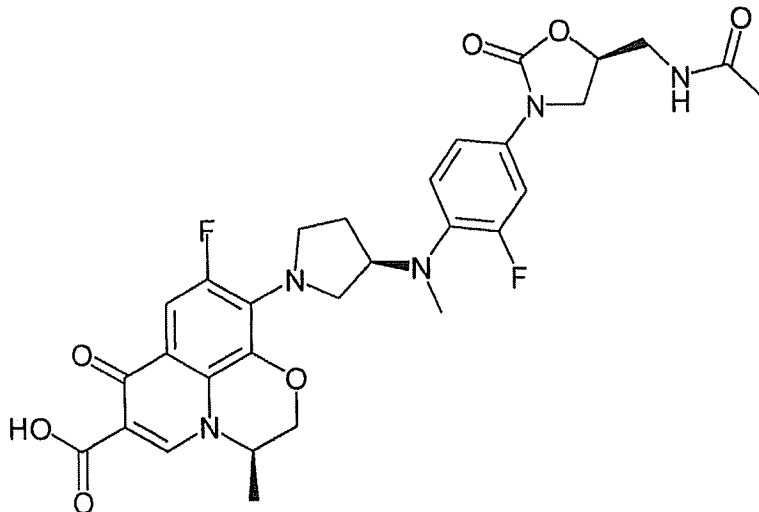
$[\alpha]^{25}_{\text{D}} = -80.6^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

EXAMPLE 34

15

9-[3-(R)-({4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid

20



Following the procedure described in Example 3 and starting with the corresponding chelate obtained by reaction of N-{3-(R)-[3-Fluoro-4-(methyl-pyrrolidin-3-yl-amino)-phenyl]-2-oxo-oxazolidin-5-(S)-ylmethyl}-acetamide (obtained following the procedure for the obtention of Reference Example No.27, but replacing 3(R,S)-aminopyrrolidine by 3-(R)-aminopyrrolidine) and 8,9-Difluoro-3-(R)-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalene-5-carboxylic acid boron difluoride chelate (obtained according to Shohgo Atarashi et al., *Chem. Pharm. Bull.* (1987), **35** (5), 1896-1902) the product of the title is obtained.

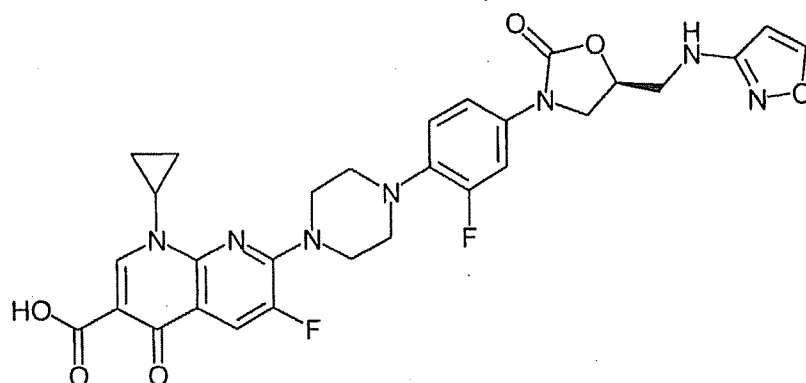
^1H -RMN (DSMO- d_6 , 200 MHz, δ (ppm)): 8.90 (s, 1H); 8.24 (t, 1H, NH); 7.60-7.40 (m, 2H); 7.36-7.10 (m, 2H); 4.95-4.80 (m, 1H); 4.80-4.60 (m, 1H); 4.54 (d, 1H); 4.30 (d, 1H); 4.10 (t, 1H), 4.00-3.30 (m, 8H); 2.72 (s, 3H); 2.20-1.80 (m, 2H); 1.84 (s, 3H); 1.42 (d, 3H).

$[\alpha]^{25}_{\text{D}} = +18^\circ$ (c 0.5, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 9/1)

20

EXAMPLE 35

1-Cyclopropyl-6-fluoro-7-(4-{2-fluoro-4-[5-(S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid



Following the procedure described in Example 14 and starting with the corresponding product obtained by reaction of the compound in reference Example 25 N-deprotected and 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid the product of the title is obtained.

¹H-RMN (DSMO-d₆, 200 MHz, δ (ppm)): 13.2 (s, 1H); 8.61 (s, 1H); 8.40 (s, 1H); 8.10 (d, 1H); 7.50 (d, 1H); 7.10 (m, 2H); 6.55 (t, 1H); 5.98 (s, 1H); 4.85 (m, 1H); 4.04 (m, 5H); 3.75 (m, 2H); 3.40 (m, 2H); 3.17 (m, 4H); 1.2 (m, 4H).

15

EXAMPLES OF PHARMACOLOGICAL RESULTS

Description of the methods used for evaluation of the pharmacological properties

20

The antibacterial activity of the new synthesised compounds on the various strains of the bacterial species was implemented using the technique of microdilution in culture broth according to the regulations of the National Committee for Clinical Laboratory Standards (NCCLS),

(NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Approved standard M7-A3. NCCLS, Vilanova. PA., and NCCLS. 1993. Methods for dilution antimicrobial susceptibility tests for anaerobic bacteria that grow aerobically. Approved standard M1-A3. NCCLS, Vilanova. PA).

The inoculum used was 5×10^5 UFC/ml following dilution of the cultures overnight in the exponential phase of bacterial growth.

The MIC expressed in mg/l was defined as the minimum concentration of antibiotic which inhibited any visible growth.

15

Linezolid was included as comparative compound.

The compounds were tested on the strains of G(+) and G(-) bacteria set out in Table 1, in which:

20

- A: *S. aureus* resistant to meticillin
- B: *E. faecalis* resistant to vancomycin
- C: *S. pneumoniae* resistant to penicillin
- D: *S. agalactiae*
- 25 E: *S. epidermidis*
- F: *S. pyogenes*
- G: *B. fragilis*
- H: *E. coli*
- I: *H. influenzae*
- 30 J: *M. Catarrhalis*.

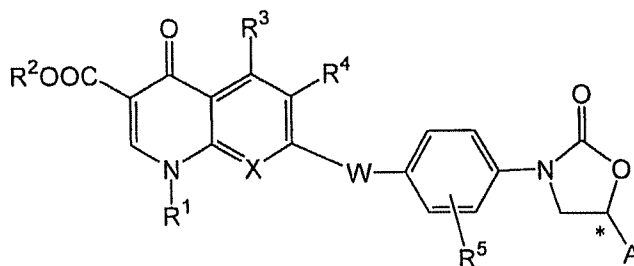
Table 1 – Antibacterial activity on hospital strains (resistant) of Gram (+) and Gram (-) bacteria

5	PRO- DUCT	G (+) strains						Anaerobic	G (-) strains		
		A	B	C	D	E	F		H	I	J
	Linezo- lid	2	2	1	2	1	1	2	>64	16	16
	EXAMP. 1 + 8	0,25	0,125	<0,125	0,125	0,125	<0,125	0,25	8	0,25	0,25
	EXAMP. 3	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	64	4	0,5
	EXAMP. 4	0,25	0,25	<0,125	<0,125	<0,125	<0,125	0,5	16	2	1
	EXAMP. 5	0,5	0,5	0,5	0,5	0,25	0,5	2	4	1	1
	EXAMP. 6	2	1	1	0,5	0,5	1	16	2	<0,125	0,25
	EXAMP. 7	0,25	0,5	0,25	0,5	0,25	0,25	2	8	4	1
	EXAMP. 9	<0,125	<0,125	<0,125	<0,125	<0,125	<0,125	0,5	>64	1	0,25
	EXAMP. 10	1	2	1	1	0,25	1	4	64	4	2
	EXAMP. 11	0,5	0,5	0,5	1	0,125	0,5	1	32	4	1
	EXAMP. 16	4	2	1	1	2	1	8	>64	>64	8
	EXAMP. 17	2	2	0,5	0,5	1	1	4	>64	64	4
	EXAMP. 19	4	8	4	8	4	8	>64	32	1	2
	EXAMP. 20	1	2	1	1	0,50	1	>64	>64	2	4
	EXAMP. 21	0,25	<0,125	<0,125	<0,125	<0,125	<0,125	0,25	64	2	0,5
	EXAMP. 22	<0,125	<0,125	0,25	<0,125	<0,125	<0,125	0,5	64	2	0,5

CLAIMS

1. Compound of general formula (I):

5



(I)

10 wherein:

X: CR⁶ or N;

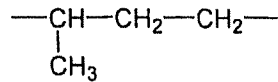
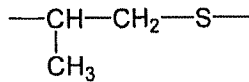
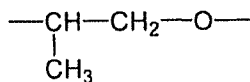
R¹: alkyl C₁-C₄, cycloalkyl C₃-C₆, alkenyl C₂-C₄, 2-
15 hydroxyethyl, 2-fluoroethyl, or phenyl optionally
substituted by 1 or 2 atoms of fluorine;

R²: H, alkyl C₁-C₄ or phenyl;

20 R³: H, halogen, alkyl C₁-C₄, or alkoxy C₁-C₄, amino;

R⁴: H or halogen;

R⁶: H, halogen, alkyl C₁-C₄, haloalkoxy C₁-C₄, or
25 else R¹ and R⁶ together form a bridge of structure



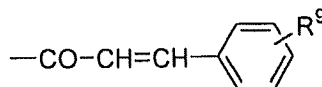
R^5 : H, halogen, OCH_3 , alkoxy $\text{C}_1\text{--C}_4$, alkyl $\text{C}_1\text{--C}_4$, or haloalkyl $\text{C}_1\text{--C}_4$;

5

A: $-\text{CH}_2\text{--NH--R}^7$, $-\text{CHOH--C}\equiv\text{CH}$;

wherein

10 R^7 : isoxazol, $-\text{CO--R}^8$, $-\text{CS--R}^8$, $-\text{CS--OR}^8$, $-\text{COOR}^8$, $-\text{CONHR}^8$, $-\text{CSNHR}^8$, $-\text{SO}_2\text{--R}^8$ or



15 wherein

R^8 : alkyl $\text{C}_1\text{--C}_4$, haloalkyl $\text{C}_1\text{--C}_4$, alkenyl $\text{C}_2\text{--C}_4$, aryl, alkyl $\text{C}_1\text{--C}_4$ substituted by an alkoxy group $\text{C}_1\text{--C}_4$, carboxyalkyl $\text{C}_1\text{--C}_4$, cyano, or amino;

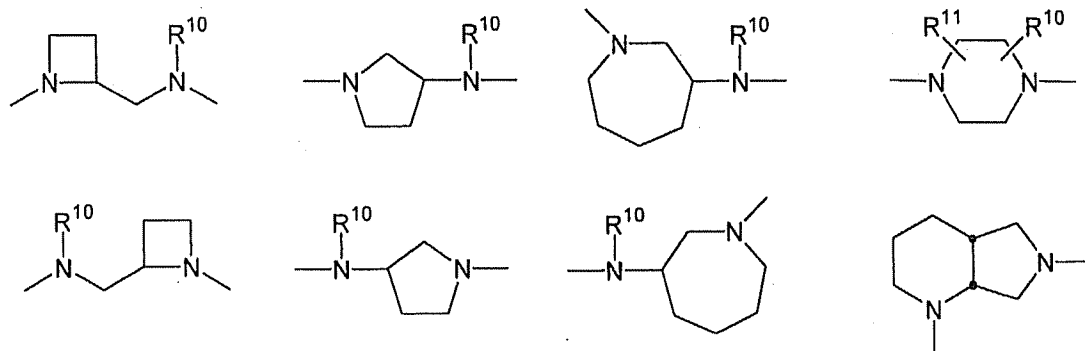
20

R^9 : H, alkyl $\text{C}_1\text{--C}_4$, alkenyl $\text{C}_2\text{--C}_4$, OH, alkoxy $\text{C}_1\text{--C}_4$, $\text{NR}^{12}\text{R}^{13}$, NO_2 , halogen, or CO--R^{12} ;

R^{12} and R^{13} : independently, H or alkyl $\text{C}_1\text{--C}_4$;

25

W:



wherein

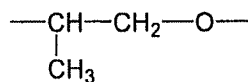
R¹⁰ and R¹¹ are independently H, or alkyl C₁-C₄;

5

a pharmaceutically acceptable salt or solvate, or any geometric isomer, optical isomer or mixture of isomers thereof in any proportion or polymorph thereof.

10 2. Compound according to Claim 1, characterised in that R¹ is cyclopropyl, ethyl, 2-fluoroethyl, phenyl or difluorophenyl, or else R¹ and R⁶ together form a bridge of structure:

15

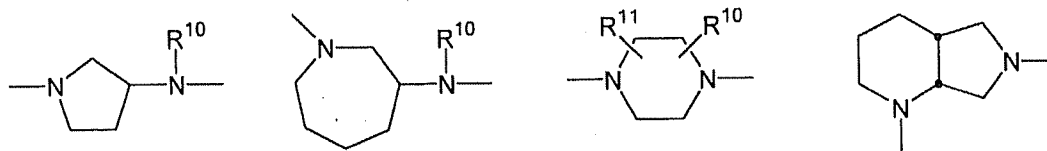


3. Compound according to Claim 1, characterised in that R⁶ is H, CH₃, OCH₃, OCHF₂, F or Cl.

4. Compound according to Claim 3, characterised in
20 that R⁶ is H or F.

5. Compound according to Claim 1, characterised in that R⁴ is F or Cl and R³ is H.

6. Compound according to Claim 1, characterised in that W is



5 wherein R^{10} and R^{11} are as defined in Claim 1.

7. Compound according to Claim 1, characterised in that the C5 of oxazolidinone ring has an (S) configuration when $A = -CH_2-NH-R^7$ and (R) when $A = -CHOH-C\equiv CH$.

10

8. Compound according to claims 1 to 6, characterised in that it is selected from one of the following:

- 15 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 7-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-azepan-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 30

- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 5 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 10 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-ureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 15 - 1-cyclopropyl-7-(4-{4-[5-(S)-(ethoxycarbonylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-{4-[2-fluoro-4-(5-(S)-{[3-(4-fluoro-phenyl)-acryloylamino]-methyl}-2-oxo-oxazolidin-3-yl)-phenyl]-piperazin-1-yl}-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 20 - 1-cyclopropyl-7-[4-(4-{5-(S)-[(3-ethyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-2-fluoro-phenyl)-piperazin-1-yl]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 25 - 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-5-[5-(R)-(1-(R,S)-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}piperazin-1-yl)-4-oxo-1,4-dihydro-
- 30 [1,8]naphthyridine-3-carboxylic acid ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8] naphthyridine-3-carboxylic acid ethyl ester

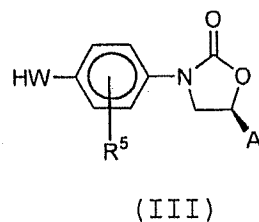
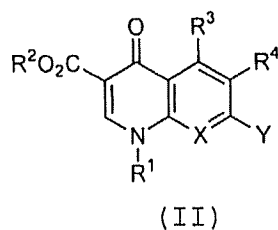
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 10 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid ethyl ester
- 1-(2,4-difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 15 (R)-(1-hydroxy-prop-2-ynyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-(2,4-difluoro-phenyl)-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-
- 20 3-carboxylic acid
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-(2,4-Difluoro-phenyl)-6-fluoro-7-(4-{2-fluoro-4-[5-
- 30 (S)-(isoxazol-3-ylaminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid
- 1-ethyl-6,8-difluoro-7-[4-(2-fluoro-4-(5-[(3-methylthioureido)-methyl]-2-oxo-oxazolidin-3-yl)-phenyl)-

- piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(3-propyl-thioureido)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 5 - 1-cyclopropyl-6-fluoro-7-[4-{2-fluoro-4-[5-(S)-(methanesulfonylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 10 - 7-(4-{4-[5-(S)-(Acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-1-ethyl-6,8-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{2-oxo-5-(S)-[(2,2,2-trifluoro-acetylamino)-methyl]-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 15 - 7-(4-{4-[5-(S)-(benzoylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro 4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
 - 20 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 25 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-
 - 30 difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6,8-

- difluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
ethyl ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-
5 oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl
ester
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-ethyl-6-fluoro-4-
oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 10 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
methyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-6-oxo-2,3-
15 dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic acid
ethyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-
20 fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
phenalen-5-carboxylic acid methyl ester
- 9-[3-({4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-methyl-amino)-pyrrolidin-1-yl]-8-
fluoro-3-methyl-6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-
25 phenalen-5-carboxylic acid ethyl ester
- 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-
6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic
acid methyl ester
- 30 - 9-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-8-fluoro-3-methyl-
6-oxo-2,3-dihydro-6H-1-oxa-3a-aza-phenalen-5-carboxylic
acid ethyl ester

- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 5 - 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 10
- 1-cyclopropyl-6-fluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester
- 15
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-[1,8]naphthyridine-3-carboxylic acid methyl ester
- 20
- 7-(4-{4-[5-(S)-(acetylamino-methyl)-2-oxo-oxazolidin-3-yl]-2-fluoro-phenyl}-piperazin-1-yl)-6,8-difluoro-1-(2-fluoro-ethyl)-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid methyl ester
- 25 - 1-Ethyl-6,8-difluoro-7-[4-(2-fluoro-4-{5-(S)-[(3-methyl-thioureido)-methyl]-2-oxo-oxazolidin-3-yl}-phenyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester

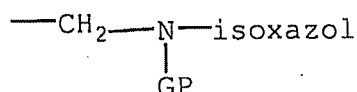
30 9. Process for obtaining a compound of general formula (I), according to Claim 1, characterised in that it comprises the reaction of a compound of general formula (II) with a compound of general formula (III):



wherein:

A' is:

- 5 a) $-\text{CH}_2-\text{NH}-\text{R}^7$
 b) $-\text{CHOH}-\text{C}\equiv\text{CH}$
 c)

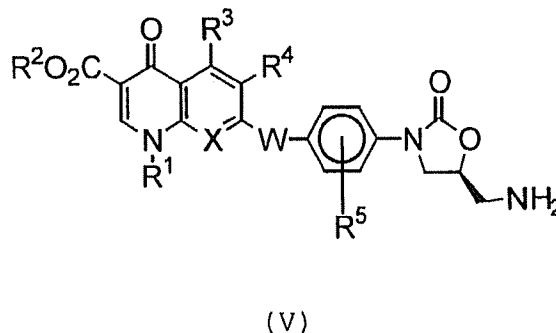


10 Y is an leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

 R¹, R², R³, R⁴, R⁵, X and W have the meaning defined in Claim 1;

15 GP is a protecting group of amines.

10. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is $-\text{CH}_2-\text{NH}-\text{R}^7$ and R⁷ is different from isoxazole, characterised in that it
 20 comprises the reaction of a compound of formula (V)



wherein R¹, R², R³, R⁴, R⁵, X and W have the meaning

defined in Claim 1.

with a compound of formula (VI) or with a compound of formula (VII)

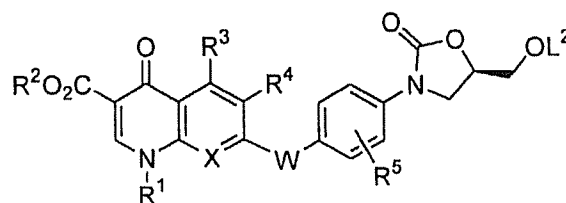


wherein L is a good leaving group, such as an atom of halogen (F, Cl, Br, I), a tosylate or mesylate group, and the like;

Z is Oxygen or Sulphur, and

R^7 and R^8 have the meaning defined in Claim 1, with R^7 being different from isoxazol.

11. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is $-CH_2-NH-R^7$ and R^7 is isoxazol, characterised in that it comprises the reaction of a compound of general formula (VIII):



(VIII)

20

wherein

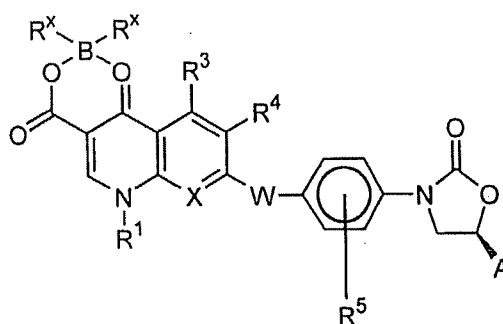
- OL^2 represents a good leaving group, such as a residue of aryl or methyl sulphonic acid, substituted or not substituted, preferably by a tosylate or mesylate group;

- R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1;

with isoxazolil-3-amine, the amine group being protected with a protecting group of amines.

30

12. Process for obtaining a compound of general formula (I), according to Claim 1, in which R^2 is hydrogen, characterised in that it comprises the hydrolysis of a boron chelate of formula (IX)



5

(IX)

wherein

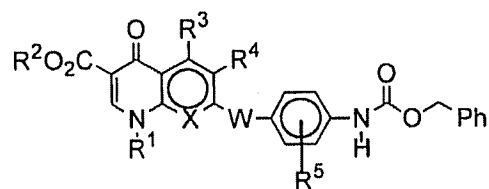
R^x can be F or CH_3COO^- ;

10 A, R^1 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

13. Process for obtaining a compound of general formula (I), according to Claim 1, in which A is

15 $-\text{CHOH}-\text{C}\equiv\text{CH}$

characterised in that it comprises the reaction of a compound of formula (IV)



(IV)

20

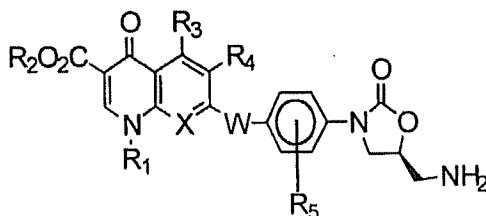
wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1,

with 2,3-hydroxy-pent-4-ynyl p-toluenesulphonate.

14. Process as claimed in any of claims 11 to 13, characterised in that it comprises subjecting the product 5 obtained, optionally, to one or more of the following final steps:

- a) Conversion of a compound of general formula (I) into another compound of general formula (I);
- b) Elimination of the protecting group;
- 10 c) Preparation of a pharmacologically acceptable salt of a compound of formula (I) and/or a pharmacologically acceptable solvate thereof.

15. Compound of formula (V)

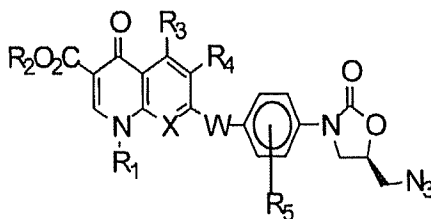


15

(V)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

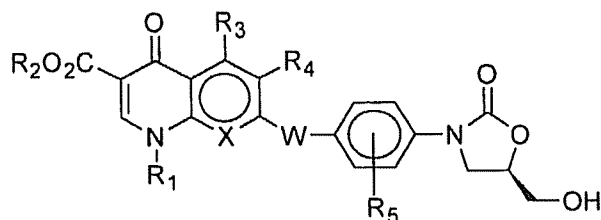
20 16. Compound of formula (X)



(X)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

17. Compound of formula (XI)



5

(XI)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , X and W have the meaning defined in Claim 1.

10 18. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8, for use as a medicament.

15 19. Use of a compound of general formula (I), according to any of claims 1 to 8, for the preparation of a pharmaceutical composition for treating microbial infections in humans or warm-blooded animals.

20 20. Pharmaceutical composition which comprises a compound of general formula (I) according to any of claims 1 to 8 in a therapeutically active quantity and with a suitable quantity of at least one excipient.

25

INTERNATIONAL SEARCH REPORT

Int. Application No

PC1/1B 02/02408

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D413/14 A61K31/422 A61P31/04 C07D471/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FR 2 403 339 A (BELLON LABOR SA ROGER) 13 April 1979 (1979-04-13) claim 1 ---	1-20
A	WO 97 37980 A (BARBACHYN MICHAEL R ;UPJOHN CO (US); FLECK THOMAS J (US); HOUSER D) 16 October 1997 (1997-10-16) claim 1 ---	1-20
A	WO 98 01447 A (DARBYSHIRE CATHERINE JANE ;ZENECA LTD (GB); BETTS MICHAEL JOHN (GB) 15 January 1998 (1998-01-15) claim 1 ---	1-20
A	WO 93 23384 A (UPJOHN CO ;HUTCHINSON DOUGLAS K (US); BRICKNER STEVEN JOSEPH (US);) 25 November 1993 (1993-11-25) claim 1 --- -/--	1-20



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search.

11 September 2002

Date of mailing of the international search report

25/09/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Baston, E

INTERNATIONAL SEARCH REPORT

Int'l Application No

PCT/IB 02/02408

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 878 194 A (SANKYO CO ;UBE INDUSTRIES (JP)) 18 November 1998 (1998-11-18) claim 1 ---	1-20
A	HAYAKAWA I ET AL: "SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF SUBSTITUTED 7-OXO-2,3-DIHYDRO-7H-PYRIDOU1,2,3-DEU1,4BE NZOXAZINE-6-CARBOXYLIC ACIDS" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 32, no. 12, 1 December 1984 (1984-12-01), pages 4907-4913, XP000654032 ISSN: 0009-2363 table 1 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/02408

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
FR 2403339	A	13-04-1979	GB 1598915 A	23-09-1981
			AU 3996278 A	27-03-1980
			CA 1175836 A1	09-10-1984
			DE 2840910 A1	05-04-1979
			ES 473486 A1	01-11-1979
			FR 2403339 A1	13-04-1979
			FR 2498931 A1	06-08-1982
			JP 1147604 C	26-05-1983
			JP 54066686 A	29-05-1979
			JP 57038581 B	16-08-1982
			NL 7809591 A ,B,	22-03-1979
			SE 444566 B	21-04-1986
			SE 7809411 A	21-03-1979
			US 4292317 A	29-09-1981
			AU 520458 B2	04-02-1982
			BE 870576 A1	19-03-1979
WO 9737980	A	16-10-1997	AT 209193 T	15-12-2001
			AU 706117 B2	10-06-1999
			AU 2318297 A	29-10-1997
			CA 2248143 A1	16-10-1997
			CN 1215393 A ,B	28-04-1999
			CZ 9802871 A3	17-02-1999
			DE 69709718 D1	21-02-2002
			DE 69709718 T2	20-06-2002
			DK 892792 T3	02-04-2002
			EP 1114819 A1	11-07-2001
			EP 0892792 A1	27-01-1999
			ES 2166073 T3	01-04-2002
			JP 2000508312 T	04-07-2000
			KR 2000005358 A	25-01-2000
			NO 984737 A	09-12-1998
			NO 20015253 A	09-12-1998
			NZ 332278 A	26-05-2000
			PL 329295 A1	15-03-1999
			PT 892792 T	31-05-2002
			RU 2176643 C2	10-12-2001
			SI 892792 T1	30-06-2002
			SK 133698 A3	11-06-1999
			TW 449593 B	11-08-2001
			US 2002095054 A1	18-07-2002
			WO 9737980 A1	16-10-1997
			US 5837870 A	17-11-1998
			ZA 9702983 A	08-10-1998
WO 9801447	A	15-01-1998	AU 3352197 A	02-02-1998
			EP 0918770 A1	02-06-1999
			WO 9801447 A1	15-01-1998
			JP 2000514084 T	24-10-2000
WO 9323384	A	25-11-1993	AT 219770 T	15-07-2002
			AU 668733 B2	16-05-1996
			AU 4287793 A	13-12-1993
			CA 2133079 A1	25-11-1993
			CN 1079964 A ,B	29-12-1993
			CZ 9402505 A3	16-08-1995
			DE 69332061 D1	01-08-2002
			EP 0640077 A1	01-03-1995

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/IB 02/02408

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323384 A		FI 945246 A	08-11-1994
		HU 72296 A2	29-04-1996
		HU 9500659 A3	28-11-1995
		IL 105555 A	15-07-1998
		JP 3255920 B2	12-02-2002
		JP 7506829 T	27-07-1995
		MX 9302665 A1	01-11-1993
		NO 944237 A	04-01-1995
		PL 174909 B1	30-10-1998
		PL 174850 B1	30-09-1998
		RU 2105003 C1	20-02-1998
		SK 133794 A3	07-06-1995
		WO 9323384 A1	25-11-1993
		US 5547950 A	20-08-1996
		US 5700799 A	23-12-1997
		ZA 9302855 A	24-10-1994
EP 0878194 A	18-11-1998	AU 713704 B2	09-12-1999
		AU 1556497 A	22-08-1997
		EP 0878194 A1	18-11-1998
		NO 983512 A	30-09-1998
		CA 2245179 A1	07-08-1997
		CN 1214632 A	21-04-1999
		CZ 9802386 A3	16-12-1998
		HU 9901642 A2	28-09-1999
		JP 9323932 A	16-12-1997
		WO 9727856 A1	07-08-1997